



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

**A Study of the Comprehensive® Shoulder System
with nano Humeral Component in Total Shoulder
Arthroplasty**

PROTOCOL NUMBER: ORTHO.CA.GE1.12

PREMARKET INVESTIGATION NUMBER: G110207

PROTOCOL VERSION: 1.3



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

GENERAL INFORMATION

STUDY SPONSOR(S): **Biomet Orthopedics, Warsaw, Indiana, USA**

PROJECT LEADER(S):

NAME	CONTACT (I.E. POSTAL ADDRESS, PHONE NUMBER)	ROLE (OVERALL/LOCAL LEADER)
Jarrold Hunnicutt, CCRA	1800 W. Center St. Warsaw, Indiana 46580 (574) 372.4062 (Office) (574) 453.7834 (Mobile) (574) 371.1027 (Fax)	Overall Project Leader



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Table of Contents

STUDY SUMMARY	6
INTRODUCTION	8
SECTION A: PURPOSE.....	9
PURPOSE/OBJECTIVES	9
RATIONALE FOR CURRENT STUDY	10
SECTION B: PROTOCOL	10
OVERALL DESIGN.....	10
STUDY GROUPS AND TREATMENTS	10
NUMBER OF PROCEDURES	10
SELECTION OF SUBJECTS	10
PATIENT POPULATION.....	13
INSTITUTIONS	13
DURATION OF THE STUDY	13
STUDY DEFINITIONS AND GLOSSARY OF ABBREVIATIONS.....	13
RANDOMIZATION.....	15
PATIENT MANAGEMENT.....	15
BILATERAL PATIENTS	18
SCHEDULE OF FOLLOW-UP ASSESSMENTS.....	18
ASSESSMENT PARAMETERS AND METHODS	18
PROTOCOL DEVIATION MANAGEMENT AND REPORTING	19
ADVERSE EVENT MANAGEMENT AND REPORTING	19
SAE REPORTING.....	20
DISCONTINUATIONS AND REVISIONS (SUBJECT WITHDRAWAL)	21
CONTROL OF INVESTIGATIONAL DEVICE	22
IMPLANT RETRIEVAL AND ANALYSIS OF REMOVED IMPLANTS	22
PRIMARY HYPOTHESES	23
CO-PRIMARY ENDPOINTS	23
SECONDARY ENDPOINTS	23
ANTICIPATED CHANGES.....	24
RADIOGRAPHIC PROTOCOL	24



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

STATISTICAL ANALYSIS PLAN	25
PRIMARY STATISTICAL HYPOTHESES AND DEFINITION OF STUDY SUCCESS.....	25
RANDOMIZATION DETAILS	26
SAMPLE SIZE CALCULATION	27
INITIAL SAMPLE SIZE CALCULATIONS AND ASSUMPTIONS.....	27
STUDY POPULATIONS.....	32
ALL ENROLLED POPULATION.....	32
ANALYSIS POPULATION.....	32
MISSING DATA AND SENSITIVITY ANALYSES	32
TESTS FOR INTERACTION.....	34
PROTOCOL DEVIATIONS.....	35
DATA COLLECTION.....	36
DATA COLLECTION TIME POINTS.....	36
INFERENTIAL METHODS.....	36
SIGNIFICANCE LEVELS.....	36
SUBJECT ACCOUNTING.....	37
MODELS FOR CONTINUOUS MEASURES	38
CATEGORICAL DATA ANALYSES.....	38
BASELINE CHARACTERISTICS.....	38
EFFICACY EVALUATIONS	38
SAFETY EVALUATIONS.....	41
ADVERSE EVENTS.....	41
DATA COLLECTION, HANDLING AND RETENTION	41
SOURCE DOCUMENTATION REQUIREMENTS	41
CASE REPORT FORMS	41
STUDY DOCUMENT RETENTION.....	42
DATA REPORTING.....	42
ETHICAL AND REGULATORY REQUIREMENTS.....	42
CODE OF CONDUCT	42
REGULATORY APPROVAL.....	42
INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEE.....	42
INFORMED CONSENT	43
SUBJECT CONFIDENTIALITY.....	43



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

SECTION C: RISK ANALYSIS.....	45
GENERAL RISKS ASSOCIATED WITH SURGERY	45
GENERAL RISKS ASSOCIATED WITH TOTAL SHOULDER REPLACEMENT	46
POTENTIAL RISKS ASSOCIATED WITH COMPREHENSIVE® SHOULDER SYSTEM WITH NANO HUMERAL COMPONENT IN TOTAL SHOULDER REPLACEMENT	47
MINIMIZATION OF RISK.....	47
SECTION D: DEVICE DESCRIPTION.....	51
DEVICE DESIGN AND DESCRIPTION.....	51
INVESTIGATIONAL DEVICE DESCRIPTION	51
CONTROL DEVICE DESCRIPTION.....	52
SECTION E: MONITORING.....	53
SECTION F: LABELING	53
PACKAGE LABEL	53
INSTRUCTIONS FOR USE (IFU)	53
SURGICAL TECHNIQUE	54
SECTION G: CONSENT MATERIALS.....	54
SECTION H: IRB INFORMATION	54
SECTION I: OTHER INSTITUTIONS.....	54
SECTION J: ADDITIONAL RECORDS AND REPORTS	54
REFERENCES.....	55
EXHIBITS	56

STUDY SUMMARY

TITLE	A Study of the Comprehensive® Shoulder System with nano humeral component in Total Shoulder Arthroplasty
DESIGN	Randomized, controlled, single-blinded, prospective, multi-center study
PURPOSE	To determine the safety and efficacy of the Comprehensive® Shoulder System with nano humeral component in total shoulder arthroplasty (TSA).
PRIMARY OBJECTIVE	This study is designed to show that the Comprehensive® Shoulder System with nano humeral component is non-inferior to the Comprehensive® Shoulder System with mini stem component with respect to three co-primary endpoints (ASES score, Radiographic Success, and Absence of Revision/Removal/UADE) at 22+ months of follow up.
PRIMARY ANALYSIS	The primary analysis will use a closed testing method in which each of the co-primary endpoints are compared (Investigational versus Control) using $\alpha=0.05$. The decision rule for inferring non-inferiority of the Investigational device to the Control device will be the rejection of the null hypothesis for all co-primary endpoints.
OUTCOME MEASURES	ASES score, Single Assessment Numeric Evaluation (SANE) Score, Constant Score, Radiographic outcome, Revisions, Unanticipated Adverse Device Events (UADEs)
POPULATION	<ul style="list-style-type: none"> 132 Comprehensive® Shoulder System with nano humeral component (investigational) 132 Comprehensive® Shoulder System with mini stem component (control)
ELIGIBILITY	<p>Inclusion (Additional criteria listed in Section B: Protocol – Inclusion Criteria):</p> <ul style="list-style-type: none"> Patients for whom the surgeon has confirmed intraoperatively, has no cyst > 1cm and not more than one cyst at the implantation site Patients with non-inflammatory degenerative joint disease including osteoarthritis. Patients where the device will be used in the correction of a functional deformity (deformities preventing congruent articulation of the glenohumeral joint) Patients with pain and/or loss of function in the shoulder for whom other treatment modalities have been unsuccessful. Patients requiring unilateral or staged bilateral shoulder arthroplasty Patient must be anatomically and structurally suited to receive the implants (humeral neck must be of sufficient diameter to implant at least the smallest nano humeral component and the humeral neck is intact). Patients who are 21-90 years of age at the time of surgery and have reached skeletal maturity. Patients with an ASES score ≤ 40. <p>Exclusion (Additional criteria listed in Section B: Protocol – Exclusion Criteria) :</p> <ul style="list-style-type: none"> Patients diagnosed with avascular necrosis or post-traumatic



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

arthritis of the humeral head

- Patients found at the time of intraoperative examination to have a single cyst >1 cm in size or multiple cysts at the implantation site
- Patient presents with shoulder joint infection, sepsis, osteomyelitis or distant foci of infections which may spread to the implant site.
- Patients with cuff tear arthropathy.
- Patients who have undergone a Hemi-, Total, or Reverse Total Shoulder arthroplasty in the affected shoulder.
- Patient presents with a malunion or non-union of the tuberosities of the proximal humerus.
- Patients with osteoporosis, osteomalacia, rheumatoid arthritis, metabolic disorders of bone, muscle or connective tissue, gross deformity or any other condition of the proximal humerus (defined as severe destruction or deformity of the proximal humerus that precludes placement of the device) that in the Investigator's medical judgment could compromise implant fixation or bone healing.
- Rapid bone destruction, marked bone loss or bone resorption apparent on roentgenogram.
- Patients with neurologic or other disorders that would either affect the stability of the shoulder prosthesis, i.e., Charcot's joint, uncontrolled seizures, etc., or would affect their capability or willingness to return to the clinic for assessments and/or follow directions.
- Bone cancer, either primary or secondary, that affects the shoulder.
- Patients presenting with symptoms of chronic steroid use. (oral steroids for a chronic condition for 12 months prior to and including the date of surgery)
- Patients with a life expectancy of less than three years.
- Patients diagnosed with severe shoulder instability
- Patients diagnosed with subscapularis incompetence
- Patients diagnosed with any condition that may limit their ability to complete the consent form or would affect their capability or willingness to return to the clinic for assessments and/or follow directions (i.e. mental illness)
- Patients with known metal allergy
- Patients who refuse to sign the IRB approved consent form
- Patients who are found intraoperatively to require a specific treatment and are unable to be randomized.

DURATION

Until the last patient enrolled in the study reaches two year (22+ month) postoperative follow-up time point or until FDA authorizes closure of the study



Study of the Comprehensive® Shoulder System with nano Humeral Component in TSA: G110207

INTRODUCTION

Modern Total Shoulder Arthroplasty (TSA) was introduced in the United States over 50 years ago¹ and has helped many patients return to function after debilitating shoulder injuries and arthritis, however, due to the unique anatomy of the shoulder, total shoulder arthroplasty has not enjoyed the very low revision rates seen in total hip and total knee arthroplasty. The first attempts to address the problems posed by shoulder anatomy relied on constraint of the glenohumeral joint. Unfortunately, the mechanical stresses of the joint resulted in multiple mechanical problems contributing to an unacceptably-high failure rate due to loosening, instability or implant failure.²

Introduction of the unconstrained shoulder in the late 1970's and 80's resolved many of the mechanical problems of the constrained shoulder; however, loosening of the glenoid component continues to be the most common reason for revision of total shoulder arthroplasties.³ Humeral loosening on the other hand has not historically been a problem. When observing complications following unconstrained TSA from 1996-2005, (2540 shoulders total), humeral loosening occurred in only 1.1% of all shoulders.³ Because humeral loosening happens so infrequently, there is a trend toward less invasive humeral components including resurfacing and short stem implants.

In the early 2000's, shoulder resurfacing arthroplasty was introduced in to the US market. This new class of devices offered the benefit of bone conservation for younger, more active patients and the possibility of easier revision. Several companies currently offer resurfacing devices including Arthrosurface (HemiCap®), Tornier (Aequalis® Resurfacing), DePuy (Global® CAP® and CAP® CTA), Ascension (Titan™) and Biomet (Copeland™ and Copeland™ EAS™). These devices have had success clinically; however total shoulder arthroplasty has consistently showed a clinical benefit over humeral head replacement only.⁴ While many of the humeral resurfacing components are cleared for total shoulder arthroplasty, utilization in this capacity is limited due to the difficulty in accessing the glenoid since the humeral head is left intact.

Multiple short stemmed humeral components for use in shoulder arthroplasty have been introduced in the U.S., including the Comprehensive® Mini and Micro stems from Biomet and the Ascend™ Shoulder from Tornier. Although these stems are more conservative than traditional length humeral stems, they still require insertion into the medullary canal, which dictates the



Study of the Comprehensive® Shoulder System with nano Humeral Component in TSA: G110207

position of the humeral head and makes accurate reproduction of the native anatomy more challenging.⁵

The Comprehensive® Shoulder System with nano humeral component addresses these issues by offering a minimally invasive humeral component that allows the surgeon to recreate the patient's natural humeral head version and inclination, while also allowing unobstructed access to the glenoid. The Comprehensive® Shoulder System with nano humeral component is an evolved design based on the Biomet TESS® shoulder that is currently marketed outside of the United States including Europe and Canada. The Comprehensive® Shoulder System with nano humeral component has a reverse morse taper locking mechanism that allows it to interface with Biomet's current offering of Comprehensive® shoulder components for enhanced flexibility in the surgical suite. The Comprehensive® nano also utilizes Biomet's proven PPS® Porous Plasma Spray technology for proximal fixation.

SECTION A: PURPOSE PURPOSE/OBJECTIVES

The purpose of this clinical investigation is to establish the safety and efficacy of the Comprehensive® Shoulder System with nano humeral component in Total Shoulder Arthroplasty. Safety and efficacy of the device will be measured by collection and analysis of the following data at the two-year or greater time point (22 months post-operative or longer):

1. American Shoulder and Elbow Surgeons (ASES) Score
2. Single Assessment Numeric Evaluation (SANE)
3. Constant Score
4. Radiographic assessment of osteolysis, radiolucencies, migration, and subsidence
5. Comparison of overall adverse event rates including rates of removal/revision and other serious adverse events.

Please refer to the Statistical Analysis Section for a description of the analyses that will be used.



Study of the Comprehensive® Shoulder System with nano Humeral Component in TSA: G110207

RATIONALE FOR CURRENT STUDY

The current study is designed to determine the safety and efficacy of the Comprehensive® Shoulder System with nano humeral component implants (investigational) by measuring clinical, radiographic and safety outcomes when compared to the Comprehensive® Shoulder System with mini stem component (control) at the two-year or later follow-up time point.

The data collected as part of this study will be used to support Pre-Market Notification (U.S.) clearance of the Comprehensive® nano Humeral shoulder system and as such will be conducted according to all relevant FDA regulations for IDE clinical trials, sponsor and IRB requirements.

SECTION B: PROTOCOL OVERALL DESIGN

The study is designed as a prospective, multi-center, randomized, single blinded, controlled study. Patients will be enrolled at a maximum of seventeen (17) centers. Patients will be evaluated pre-operatively and at 6 weeks, 3 months, 1 year, 2 years and annually thereafter until the last patient entered into this study has completed their 2-year evaluation.

STUDY GROUPS AND TREATMENTS

Patients will be randomized to either the Comprehensive® Shoulder System with nano humeral component (investigational) or the Comprehensive® Shoulder System with mini stem component (control) group. Patients will be randomized using a 1:1 (Investigational: Control) blocked randomization plan. The treatment assignment will be revealed intraoperatively. Every attempt will be made to blind patients to their treatment until the end of the study. If a patient is revised or withdraws consent and at the request of the patient, blinding may be discontinued as no further data will be collected.

NUMBER OF PROCEDURES

A total of 264 subjects will be enrolled in this study (132 Control and 132 Investigational).

SELECTION OF SUBJECTS

All subjects considered for participation in the study will be assessed according to pre-determined eligibility criteria, listed below. All subjects considered for enrollment must be



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

recorded on the Subject Screening Log (see Exhibit 11), including patients who are considered but not consented, consented but not randomized and consented and randomized.

Inclusion Criteria

- Patients with non-inflammatory degenerative joint disease including osteoarthritis.
- Patients where the device will be used in the correction of a functional deformity, specifically deformities that prevent congruent articulation of the glenohumeral joint. Examples include but are not limited to: humeral head structural deformity, osteophyte formation restricting range of motion, etc.
- Patients with pain and/or loss of function in the shoulder for whom other treatment modalities have been unsuccessful. Examples include but are not limited to: activity modification, physiotherapy, and anti-inflammatory or other types of medication.
- Patients requiring unilateral or staged bilateral shoulder arthroplasty
- Patient must be anatomically and structurally suited to receive the implants. During the pre-operative templating, it must be confirmed that the humeral neck is of sufficient diameter to implant at least the smallest nano humeral component and that the humeral neck cortex is intact.
- Patients who are 21-90 years of age at the time of surgery.
- Patients who are skeletally mature
- Patients with an ASES score ≤ 40 .
- Patients who are willing and able to return for scheduled follow-up evaluations
- Patients who have completed a valid, IRB approved Informed Consent Form
- Patients for whom the surgeon has confirmed intraoperatively has no cyst $> 1\text{cm}$ and not more than one cyst at the implantation site
- Patients who agree to be blinded to treatment until evaluations are completed at the 22+ month endpoint.

Exclusion Criteria

- Patients diagnosed with avascular necrosis or post-traumatic arthritis of the humeral head
- Patient presents with shoulder joint infection, sepsis, osteomyelitis or distant foci of infections which may spread to the implant site.
- Patients with cuff tear arthropathy.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

- Patients who have undergone a Hemi-, Total, or Reverse Total Shoulder arthroplasty in the affected shoulder.
- Patient presents with a malunion or non-union of the tuberosities of the proximal humerus.
- Patients with osteoporosis, osteomalacia, rheumatoid arthritis, metabolic disorders of bone, muscle or connective tissue, gross deformity or any other condition of the proximal humerus (defined as severe destruction or deformity of the proximal humerus that precludes placement of the device) that in the Investigator's medical judgment could compromise implant fixation or bone healing.
- Rapid bone destruction, marked bone loss or bone resorption apparent on roentgenogram.
- Patients with neurologic or other disorders that would either affect the stability of the shoulder prosthesis, i.e., Charcot's joint, uncontrolled seizures, etc.
- Patients diagnosed with any condition that may limit their ability to complete the consent form or would affect their capability or willingness to return to the clinic for assessments and/or follow directions (i.e. mental illness).
- Bone cancer, either primary or secondary, that affects the shoulder.
- Patients presents with symptoms of chronic steroid use as defined as use of oral steroids for a chronic condition for 12 months prior to and including the date of surgery (inhaled and topical steroid usage is allowed).
- Patients with a life expectancy of less than three years.
- Patients diagnosed with severe shoulder instability
- Patients diagnosed with subscapularis incompetence
- Patients with active medico-legal activity regarding the index shoulder
- Patients known to be pregnant, planning to get pregnant, a prisoner, and/or alcohol or drug abuser
- Patients known to be involved in worker's compensation litigations regarding index shoulder
- Patients with known metal allergy
- Patients who refuse to sign the IRB approved consent form.
- Patients who are found intraoperatively to require a specific treatment and are unable to be randomized



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

- Patients, found at the time of intraoperative examination to have a single cyst >1cm in size or multiple cysts at implantation site

NOTE: Patients with a previous total shoulder replacement of the contralateral shoulder are eligible for participation in the study. However, the patient and surgeon must allow for at least 9 months between procedures.

PATIENT POPULATION

A study population of 132 investigational shoulders and 132 control shoulders undergoing primary total shoulder arthroplasty for any of the diagnoses in the Inclusion Criteria will be included in this study. All patients, regardless of sex, race, or geographic location must meet all the eligibility criteria. All patients must sign an Informed Consent to be enrolled into the study. The study requires that bilateral patients must be staged so, a separate Informed Consent must be completed for each operative side.

INSTITUTIONS

A maximum of 17 investigational sites will enroll patients into the study.

DURATION OF THE STUDY

Patient recruitment is expected to take place over a period of 24 months and all patients are to be followed annually until the last patient enrolled reaches the 2-year follow-up time point. Therefore, some patients will be evaluated for 3-5 years post-operatively or longer, depending on the length of enrollment.

STUDY DEFINITIONS AND GLOSSARY OF ABBREVIATIONS

Withdrawal: Patients who die or who formally withdraw their consent (in writing) to additional follow up. Patients who have had all components removed or humeral stem components removed.

Missing Data: Patients who refuse to return for follow-up or who cannot be located and/or do not formally withdraw consent are described as “missing data.” Sites will be instructed to continue efforts to contact these patients. See Statistical Plan for more information on how missing data will be handled in the analysis.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Osteolysis: As defined in Exhibit 3: Radiographic Protocol.

Other Interventions: This category includes other surgeries the patient incurs while enrolled in the study that are seemingly unrelated to the implanted device. This would include surgeries such as cholecystectomy, appendectomy, coronary artery bypass surgery, etc.

Revision: A procedure that removes part of the original implant configuration, with or without replacement of the entire component configuration.

Removal: A procedure where the entire original system configuration is removed.

Reoperation: Any surgical procedure that does not include removal or revision, for example, drainage of a hematoma at the surgical site.

Screen Failure: A patient who is either screened but not consented, consented but not randomized or randomized but does not receive the investigational or control device.

Adverse Event (AE): Any event occurring in a study subject that, in the opinion of an M.D. or other qualified and trained medical professional, represents an untoward medical occurrence that differs in either nature, severity, or frequency from a normal post-operative finding. AEs may not have an apparent causal relationship with the device. An AE can therefore be any discrete or ongoing unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product.

Serious Adverse Event: Any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization* or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect

*A planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health is not considered to be a serious adverse event.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Unanticipated Adverse Device Event: any serious adverse event that is or may possibly be related to the device other than those listed in Section C: Risk Analysis or in the institution's approved Informed Consent.

Abbreviations:

IRB: Institutional Review Board

ASES: American Shoulder and Elbow Surgeons Score

SANE: Single Assessment Numeric Evaluation

CRF: Case Report Form

RANDOMIZATION

The randomization plan will be produced using SAS v 9.2 for Windows. The sponsor will review preoperative paperwork; Informed Consent, Historical Record, and pre-operative American Shoulder and Elbow Surgeons Score prior to enrollment in the study and approve randomization for a subject based on those criteria that are evaluated and confirmed during or prior to the pre-operative visit. Control and accountability of the humeral investigational device will be managed in accordance with Sponsor SOPs.

Randomization must not occur until the surgical procedure has commenced, and the Intraoperative assessment of inclusion/exclusion criteria is completed. Patients who have met all eligibility criteria following the intraoperative assessment, and have signed the IRB-approved informed consent will be randomly assigned to one of two treatment groups. Patients will be randomized using a 1:1 blocked randomization scheme for investigational: control devices. Bilateral patients will be randomized by shoulder. See the Statistical Analysis Plan section for a specific description of the randomization scheme.

PATIENT MANAGEMENT

Table 1 summarizes the case report forms (CRFs) required during the course of the study. All surgery and follow up case report forms are recommended to be sent to Biomet Manufacturing Corp. within 2 weeks of the patient's operative/follow-up evaluation date. All Serious Adverse Events must be sent within 24 hours of the investigator's awareness of the event.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Pre- and post-operative clinical data will be collected by trained, authorized study personnel with the exception of patient-reported outcome assessments. Exhibit 11 contains an example of the Study Signature Log that will be utilized to document authorized study personnel. Clinical and patient reported outcomes will be collected on Case Report Forms (CRFs), as summarized in Table 1. Case Report Forms or checklists/worksheets may be used as source documentation when a complete source does not otherwise exist at the site.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Table 1: Screening and Follow-Up Clinical and Radiographic Exams						
Action	Pre-Operative	Intra-Operative	6-Weeks	3-Months	1-Year	2-Years annually thereafter***
Obtain written informed consent	x					
Complete subject screening and enrollment log	x					
Complete eligibility checklist	x					
Complete Patient History Form: HX100	x					
Complete ASES Assessments: ASES100	x		x	x	x	x
Complete SANE Assessment: SANE100			x	x	x	x
Complete Constant Score Form: CST100	x		X**	x	x	x
Randomize Patient		x				
Record Operative Details: OP100		x				
Collect Radiographic Images (AP Int., AP Ext, and Axillary Views)			x	x	x	x
Protocol Deviation Form: PD100	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>
Complete Adverse Event Form: AE100 and/or Serious Adverse Event SAE100	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>
Complete patient Withdrawal Form: WD 100		<i>As needed</i>	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>
Complete Device Revision/Removal: RR100			<i>As needed</i>	<i>As needed</i>	<i>As needed</i>	<i>As needed</i>

Each follow-up visit time point will be determined based on the date of surgery.

** At the 6 week interval, in order to protect the subscapularis repair, the strength and ROM sections are not to be completed by sites.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

*** Annual follow up will continue until study closure or until the last enrolled patient reaches their 2 year follow up window.

BILATERAL PATIENTS

A patient undergoing staged bilateral surgery must sign a consent form **for each study procedure**. Each study shoulder will be randomized separately. Bilateral patients will be required to wait at least 9 months between procedures for the purposes of the study.

Patients with staged bilateral study implants will require two ASES, Constant Score, and SANE assessment forms to allow individual assessment of each operative side over the course of the study. Patients must be instructed to assess each shoulder individually, i.e., only record right-shoulder pain levels on the CRF for their right shoulder and only report left shoulder pain on the CRF for the left shoulder.

SCHEDULE OF FOLLOW-UP ASSESSMENTS

Post-operative clinical and radiographic evaluations will be performed according to the following schedule, with the associated visit windows:

- 6 weeks (\pm 2 weeks)
- 3 months (\pm 2 weeks)
- 1 year (\pm 2 months)
- 2 years (\pm 2 months)
- Annually thereafter* (\pm 2 months)

* Until all patients reach the 2-year visit window or the study is closed

ASSESSMENT PARAMETERS AND METHODS

Pre-Operative Visit - Medical History, Demographic Data and Patient Eligibility

Demographic information will be collected so that valid comparisons can be made between the control and investigational groups. Detailed medical history will be obtained in accordance with the physician's clinic practice.

Eligibility will be determined by the collection of medical history, intraoperative criteria, and any other tests deemed relevant by the investigator and/or his or her institutional review board. Any tests that are to be conducted that are NOT part of the investigator's



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

normal clinical practice but are specific to this clinical study must be done after the patient has reviewed and signed the approved Informed Consent Form.

Clinical and Operative Assessments

An Operative Record Case Report Form will be completed to record details of group assignment, components implanted, and any operative complications.

Post-operative clinical data will be collected utilizing recognized, validated scoring systems (ASES, Constant, and SANE scores). Radiographic images and Adverse Event data will be collected and submitted to the sponsor for independent assessment.

Radiographic Assessments

Three views are required for each study shoulder at each postoperative time point; glenohumeral Anterior-Posterior (AP) in internal and external rotation and axillary radiographs. All radiographic images will be assessed for radiolucencies, osteolysis, and component movement (subsidence, migration) by a centralized independent radiographic reviewer, utilizing the 6-week visit as the baseline radiograph.

PROTOCOL DEVIATION MANAGEMENT AND REPORTING

Any deviation from the FDA and IRB-approved study protocol or any other applicable regulatory requirements is considered a protocol deviation and must be reported to the sponsor using the Protocol Deviation Case Report Form (PD-100) as soon as they are known by the investigator.. Any Protocol Deviation will be assessed for effect on patient safety or the validity of the data. Please refer to the Statistical Analysis Plan section for details on how protocol deviations will be analyzed. According to 21 CFR Part 812.150(a)(4), an investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred.

ADVERSE EVENT MANAGEMENT AND REPORTING

The sponsor requires that all adverse events, regardless of relationship to the device, and including details of the nature, onset, duration, severity, relationship to the operative procedure, relationship to the device and outcome are reported to the sponsor so that an adequate determination of device safety can be made. The following reports must be submitted:



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

- Non-serious adverse events: regardless of relationship to the investigational/control procedure/device must be recorded on the Adverse Event Form (AE100). Expected post-operative complications such as constipation and blood loss will not be counted as Adverse Events unless these events occur in greater frequency or severity than in the normal individual post-operative course (i.e. blood loss > 2 units).
- Serious Adverse Events regardless of relationship to the investigational/control procedure/device must be reported to the sponsor on the SAE reporting form (SAE100) within 24 hours of the investigator's awareness of the event. From the information included on the SAE100 form and from any other relevant information collected, the sponsor/sponsor's agents will determine which SAEs meet the definition of an unanticipated adverse device event.
- For those Serious Adverse Events determined to be unanticipated adverse device events (UADE), reports must be sent to the reporting IRB no later than ten (10) days after the date the adverse event was discovered. Once the sponsor has become aware of the UADE, the sponsor has 10 working days to report this information to FDA.

*

SAE REPORTING

Patients who have a serious adverse event, which includes patients who die or have any study component removed or revised during the course of the investigation must be reported to the sponsor. Investigators must also report these events to their governing IRB as required by IRB guidelines.

Serious adverse events are those that result in death, are immediately life threatening, requires hospitalization (or a prolongation of hospitalization in already hospitalized patients), results in a persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect.

- **Life threatening**

A life-threatening event is one where the patient is in immediate danger of death unless intervention is done. It does not mean that the patient may die at some time in the future from the event or may have died if the event had been more serious or specific.

- **Significant Disability**

A significant disability is one that causes substantial disruption to the person's normal life and activity.

The investigator or designee must complete the SAE reporting (SAE100). Then relative to the event, a Revision/Removal Form (RR 100), and/or the Withdrawal Form (WD100) form should be completed. See the Implant Retrieval and Analysis of Removed Implants section below for instructions on how to handle investigational devices that are removed from study subjects.

DISCONTINUATIONS AND REVISIONS (SUBJECT WITHDRAWAL)

It is recognized that the subject's participation in this trial is entirely voluntary, and that she/he may refuse to participate and may withdraw from participation at any time without jeopardy to any future medical care. Device Revision or Removal is also considered a withdrawal event when all components are removed, or if only the humeral stem is removed. No additional study follow-up is necessary. In the event that a patient receives a partial revision (not all components/humeral stem), a revision/removal form should be completed, but the patient should still be followed per protocol. Do not complete a withdrawal form for these patients.

Enrollment for this study is defined as receipt of either a control or an investigational device.

Therefore:

- Subjects withdrawn from the study after receipt of either the control or investigational device will NOT be replaced.
- Randomized patients who do not ultimately receive the control or investigational device:
 1. *WILL* be replaced, but
 2. Randomization assignment will not be re-used
- ***All*** subject withdrawals must be documented on the Withdrawal Form (WD100).



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

- Includes randomized patients who do not ultimately receive the control or investigational device configurations.
- If withdrawal is due to device removal or revision, the SAE 100 form must be completed. The Revision/Removal form (RR 100) should be completed in all cases including device removal details, if known.

Copies of all Case Report Forms are included in Exhibit 4.

CONTROL OF INVESTIGATIONAL DEVICE

Investigational components (nano humeral component) will be provided in implant loaner sets that are released from the sponsor's facility for each particular case. Biomet will not release an investigational device loaner set until a copy of the signed and completed informed consent form and pre-operative forms are received and reviewed for completeness and compliance with pre-operative patient eligibility criteria. Other components that comprise the investigational or control device configuration and are currently cleared for US market use may be included in the loaner set at the discretion of Biomet. Sites are allowed to utilize their general inventory supply of the cleared components (mini stem, humeral head, hybrid glenoids) identified in Exhibit 12- Component Listing and protocol Section D: Device Description. The inventory of all devices, with the exception of the nano humeral component, will not be tracked. Any use of a device not having a part number listed in Exhibit 12 will result in a protocol deviation.

Site representatives will be instructed to return the investigational device loaner sets after each surgery unless they have received written consent from Biomet to keep the loaner set for a surgery scheduled on the following day(s).

Investigators are required to retain records of device shipment, custody transfer, allocation and device return in accordance with 21CFR Part 812.140 (a).

IMPLANT RETRIEVAL AND ANALYSIS OF REMOVED IMPLANTS

All available explanted investigational devices must be returned to Biomet. All available retrieved study implants will be handled and analyzed according to the ASTM Standard F-561-97 (Reapproved 2003) and according to the most current version of the sponsor procedure 48- Procedure for Handling of Potentially Infectious Tissues, Explants, and Instruments (Exhibit 1)



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

and Procedure 52-Procedure for Analyzing Returned Explants (Exhibit 2). The address for return of the item is:

Biomet Manufacturing
Attn: AT Lab/Building C/Decontamination
nano IDE Study
56 East Bell Drive
Warsaw, IN 46582

If there are any questions regarding the return of this device, please contact the Comprehensive® nano IDE study manager at 1-800-348-9500.

PRIMARY HYPOTHESES

This study is designed to demonstrate non-inferiority of the Comprehensive® Shoulder System with nano humeral component to the control devices with respect to three co-primary endpoints at 22+ months.

CO-PRIMARY ENDPOINTS

The three co-primary endpoints for this study are:

- a. ASES score at 22+ Months
- b. No unanticipated device-related adverse event, and no fracture, perforation of the bone or joint dislocation, and no fracture, perforation or dissociation of the device, and no revision or removal of any component, and
- c. Radiographic Success, as defined by:
 - a. Subsidence of the humeral component < 5 mm, and
 - b. Migration of the humeral component < 5mm, and
 - c. No progressive lucency around the humeral component >2mm in two or more contiguous zones
 - d. Migration of the glenoid component <5 mm, and
 - e. No progressive lucency >2mm around the entire glenoid component

SECONDARY ENDPOINTS

The data collected will also be analyzed for the following secondary endpoints:



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

1. American Shoulder and Elbow Surgeon's Score (ASES) at all time points
2. Single Assessment Numeric Evaluation (SANE) Score at all time points
3. Constant Score at all time points, except 6 weeks (adjusted for age and gender)
4. Radiographic assessment of radiolucencies and subsidence
5. Overall adverse events including removal/revision and other serious adverse events

The safety of the system will be monitored by recording adverse events including serious adverse events not considered UADEs throughout the follow-up period. Types of events to be collected include but are not limited to:

- Device removal or revisions
- Unanticipated adverse device events
- Systemic adverse events
- Local adverse events
- Reoperations and Other Interventions

Study participants will only be considered discontinued/withdrawn for the following reasons:

- Death
- Withdrawal of consent (written)
- Revision/Removal

Information from any patient who fails to return for multiple, consecutive, scheduled follow-up visits for any reason other than the criteria listed above will be identified as Missing Data.

ANTICIPATED CHANGES

It is possible that during the course of the study, certain changes may become desirable, although none are anticipated at this time. All changes to the investigation require prior approval from the investigator's Institutional Review Board (IRB) or Ethics Committee (EC) and if necessary, the FDA. Any other deviation from the stated protocol will be considered as such and will be reported accordingly. Since TSA is an elective procedure, it is not expected that treatment will require administration in an emergency setting, therefore all changes to the protocol require review and approval by the investigator's IRB prior to implementation.

RADIOGRAPHIC PROTOCOL



Study of the Comprehensive® Shoulder System with nano Humeral Component in TSA: G110207

A detailed radiographic protocol is contained in Exhibit 3.

STATISTICAL ANALYSIS PLAN

This is a two-group, multi-center, randomized single blinded clinical trial to compare Total Shoulder Arthroplasty with Biomet's Comprehensive® Shoulder System with nano humeral component to another active intervention, a Total Shoulder Arthroplasty with Comprehensive® Shoulder System with mini stem component (abbreviations: Investigational vs. Control).

PRIMARY STATISTICAL HYPOTHESES AND DEFINITION OF STUDY SUCCESS

This study is designed to show that the Investigational device is non-inferior to the control device using three co-primary study endpoints. This will be shown using a closed testing method in which each of the primary endpoints specified below are compared using $\alpha=0.05$. Study success requires that the Investigational group successfully demonstrate non-inferiority when compared to the Control group for all three of the individual primary endpoints, using the statistical methods described below. Because non-inferiority must be successfully shown for all three endpoints for study success, the type I error rate is preserved at 5% for the entire primary endpoint.¹

The individual non-inferiority hypotheses for each of these three tests are as follows:

Radiographic Success

The proportion of successful outcomes (i.e., patients meeting radiographic success criteria) in the Investigational group is non-inferior to the proportion of successful outcomes in the Control group using a 10% margin of non-inferiority. The test is based on the lower bound of a one-sided 95% confidence interval for the difference, Investigational minus Control, in proportions of success at 22+ months. A conclusion of non-inferiority is supported if the lower bound of the confidence interval is at least -0.10.

Absence of Revision/Removal/UAE

¹ Dmitrienko, Alex, et al. *Analysis of Clinical Trials Using SAS*. SAS Publishing, 2005, pp75-76.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

The proportion of successful outcomes (i.e., patients not requiring a revision/removal of any device component or receiving a UADE during the course of the study) in the Investigational group is non-inferior to the proportion of successful outcomes in the Control group using a 10% margin of non-inferiority. The test is based on the lower bound of a one-sided 95% confidence interval for the difference, Investigational minus Control, in proportions of success at 22+ months. A conclusion of non-inferiority is supported if the lower bound of the confidence interval is at least -0.10.

American Shoulder and Elbow Surgeons Score

The mean American Shoulder and Elbow Surgeons (ASES) Score for the Investigational group is non-inferior to the mean ASES score for the Control group using a 9.5-point margin of non-inferiority. This margin is based on an approximation that is sometimes used for the MCID based on the observation that for many patient-reported outcome measures, the MCID is about half the SD of change². This method is mentioned as well in an article by Singh et. al, where a half-standard deviation is mentioned as a generally accepted clinically significant benchmark³. Information about plausible values of the standard deviations ASES scores are available in an article by Angst, et. al.⁴ This article gives a standard deviation of postoperative ASES score for 142 subjects of 19.0 points, giving a half-standard-deviation of 9.5 points.

This test will be based on the lower bound of a one-sided 95% confidence interval for the difference, Investigational minus Control, in means at 22+ months. A conclusion of non-inferiority is supported if the lower bound of the confidence interval is at least -9.5 points.

RANDOMIZATION DETAILS

² Murray et al. "The use of the Oxford hip and knee scores." *JBJS(Br)*. 2007; 89-B 1010-14.

³ Singh, Jasvinder et. al. "Challenges with health-related quality of life assessment in arthroplasty patients: Problems and solutions". *J Bone Joint Surg* 2010; 18:72-82.

⁴ Angst et. al. "Responsiveness in Shoulder Arthroplasty Outcome Instruments." *Arthritis & Rheumatism (Arthritis Care & Research)* Vol. 59, No. 3, March 15, 2008, pp 391-398



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Balanced, blocked randomization (1:1, Investigational: Control) will be implemented. Randomization will be per shoulder, and each shoulder will count as a separate case toward the total sample size. In the event that a screen failure occurs post-randomization, randomization will not be reassigned and this shoulder will not count toward the overall sample size. Randomization will continue with the next shoulder enrolled as previously described until the minimum sample size is reached in both treatment groups. Randomization will be blocked by site, and each site will receive separate randomization plans using a predetermined block size that will remain undisclosed to the sites.

SAMPLE SIZE CALCULATION

INITIAL SAMPLE SIZE CALCULATIONS AND ASSUMPTIONS

The primary objective of this study is to show that the Investigational device is non-inferior to the Control device with respect to three co-primary endpoints at 22+ months. The sample size for each endpoint was calculated, and the largest chosen as the sample size for this study. The endpoint requiring the largest sample size was Radiographic Success; therefore the sample size for this study will be the one described immediately below. For reference, the sample size for the other two endpoints is shown as well.

Radiographic Success

Non-inferiority sample size calculations were implemented in nQuery Advisor 7.0 software using a 1:1 ratio of Investigational to Control subjects. This software uses methodology as described in a text by Farrington and Manning⁵.

The sample size needed to obtain 90% power for testing for non-inferiority of the investigational device to the control device with regard to radiographic success was calculated as follows:

⁵ Farrington and Manning. "Test statistics and sample size formulae for comparative binomial trials with null hypotheses of non-zero risk difference for non-unity relative risk". *Statistics in Medicine* 9(1990) pp 1447-1454.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Definitions:

p_I : Proportion of Radiographic success in the Investigational treatment group

p_C : Proportion of Radiographic success in the Control treatment group.

δ : Non-inferiority margin. Lower 95% confidence bound for difference in proportions of clinically successful subjects at 22+ months (Investigational – Control) must be greater than $-\delta$.

For a specified constant, $0 < \delta < 1$, the hypotheses of non-inferiority are:

$$H_0: p_I - p_C \leq -\delta \text{ vs. } H_A: p_I - p_C > -\delta.$$

Information on plausible values of the percentage of patients projected to be radiographic failures was found by looking in the literature to find plausible rates for each component of the radiographic failure definition. Subsidence and migration of the humeral component and progressive radiolucency around the humeral component have been reported at approximately 2% and 0%, respectively. Migration of the glenoid component and progressive lucency of the glenoid component have been reported at approximately 5% and 6%, respectively⁶. Because some overlap is to be expected, the overall Radiographic Success rate is estimated to be 93% for sample size calculation purposes.

Assumptions:

$\alpha = 0.05$	Probability of Type I error
$\beta = 0.10$	Probability of Type II error: power = $1 - \beta$
$p_C = p_I = 0.93$	Estimated success rate for Control and Investigational groups
$\delta = 0.10$	Non-inferiority Margin

⁶ Sperling, et al. "Radiographic assessment of ingrowth total shoulder arthroplasty." *JBJS*. November/December 2000, Vol 9 No. 6, p 507-513.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Resulting sample sizes (number of shoulders), not adjusted for attrition, are 112 Investigational vs. 112 Control (5% type I error rate, 90% power). The sample size was increased by 15% to allow for possible attrition. This gives a sample size of 264 total subjects (132 Investigational and 132 Control).

Absence of Revision/Removal/UAE

Non-inferiority sample size calculations were implemented in nQuery Advisor 7.0 software using a 1:1 ratio of Investigational to Control subjects. This software uses methodology as described in a text by Farrington and Manning⁷.

The sample size needed to obtain 90% power for testing for non-inferiority of the investigational device to the control device with regard to Absence of Revision/Removal/UAE was calculated as follows:

Definitions:

p_I : Proportion of shoulders in the Investigational treatment group without a Revision/Removal/UAE

p_C : Proportion of shoulders the Control treatment group without a Revision/Removal/UAE

δ : Non-inferiority margin. Lower 95% confidence bound for difference in proportions of clinically successful subjects at 22+ months (Investigational – Control) must be greater than $-\delta$.

For a specified constant, $0 < \delta < 1$, the hypotheses of non-inferiority are:

$$H_0: p_I - p_C \leq -\delta \text{ vs. } H_A: p_I - p_C > -\delta.$$

Information on plausible values of the percentage of patients with a revision was found in an article by Jost, et. al. on subjects with Biomet Comprehensive mini-stem shoulder device⁸. A

⁷ Farrington and Manning. "Test statistics and sample size formulae for comparative binomial trials with null hypotheses of non-zero risk difference for non-unity relative risk". *Statistics in Medicine* 9(1990) pp 1447-1454.

total of 49 patients underwent shoulder replacements with the TESS humeral prosthesis with minimum follow-up 2 years. One implant was revised, resulting in a revision rate of 2.0%.

Fracture/perforation of bone, joint dislocation, and dissociation of the device have been reported at approximately 2%⁹, 1%^{10 11}, and 0¹²% respectively. Fracture/perforation of the device is not expected to occur and so is estimated at 0%, Using this information, overall success rate is estimated to be 95% (2%+2%+1%) for sample size calculation purposes.

Assumptions:

$\alpha = 0.05$	Probability of Type I error
$\beta = 0.10$	Probability of Type II error: power = $1 - \beta$
$p_C = p_I = 0.95$	Estimated success rate for Control and Investigational groups
$\delta = 0.10$	Non-inferiority Margin

Resulting sample sizes (number of shoulders), not adjusted for attrition, are 82 Investigational vs. 82 Control (5% type I error rate, 90% power). The sample size was increased by 15% to allow for possible attrition. This gives a sample size of 194 total subjects (97 Investigational and 97 Control).

⁸ Jost, Patrick et. al. "Total Shoulder Arthroplasty Utilizing Mini-Stem Humeral Componts: Technique and Short-Term Results." *Hospital For Special Surgery Journal* (2011).

⁹ Bohsali, et. al. "Complications of Total Shoulder Arthroplasty." *JBJS*. 2006 Volume 88-A Number 10, p 2279-2292.

¹⁰ Pfahler, et. al. "Hemiarthroplasty versus total shoulder prosthesis: Results of cemented glenoid components." *J Shoulder Elbow Surg* March/April 2006, p 154-163.

¹¹ Boyd, et. al. "Total Shoulder Arthroplasty vs Hemiarthroplasty." *Journal of Arthroplasty*. December 1990, Vol 5 No. 4, p 329-336.

¹² Blevins, et. al. "Dissociation of modular humeral head components: A biomechanical and implant retrieval study." *J Shoulder Elbow Surg* March 1997, Volume 6 Issue 2, p A1.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

American Shoulder and Elbow Surgeons(ASES) Score

Non-inferiority sample size calculations were implemented in nQuery Advisor 7.0 software using a 1:1 ratio of Investigational to Control subjects. This software uses methodology of the two-group t-test of equivalence in means as described in a text by Dixon and Massey⁸ as well as in a text by O'Brien and Muller.⁹

The sample size needed to obtain 90% power for testing the hypothesis above was calculated as follows:

Definitions:

μ_I : Mean ASES score for the Investigational (Stemless Shoulder) treatment group.

μ_C : Mean ASES score for the Control (Total Shoulder) treatment group.

δ : Non-inferiority margin. Lower 95% confidence bound for difference in mean ASES scores at 22+ months (Investigational – Control) must be greater than $-\delta$.

For a specified constant, $0 < \delta < 1$, the hypotheses of non-inferiority are:

$$H_0: \mu_I - \mu_C \leq -\delta \text{ vs. } H_1: \mu_I - \mu_C > -\delta.$$

Information about plausible values of the standard deviations ASES scores are available in an article by Angst, et. al.¹³ This article gives a standard deviation of postoperative ASES score for 142 subjects of 19 points.

Assumptions:

$\alpha = 0.05$ Probability of Type I error

$\beta = 0.10$ Probability of Type II error: power = $1 - \beta$

¹³ Angst et. al. "Responsiveness in Shoulder Arthroplasty Outcome Instruments." Arthritis & Rheumatism (Arthritis Care & Research) Vol. 59, No. 3, March 15, 2008, pp 391-398.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

$s_C = s_I = 19$	Estimated standard deviation of ASES scores for Control and Investigational groups
$\delta = 9.5$	Non-inferiority Margin

Resulting sample sizes (number of shoulders), not adjusted for attrition, are 70 Investigational vs. 70 Control (5% type I error rate, 90% power). The sample size was increased by 15% to allow for possible attrition. This gives a sample size of 166 total subjects (83 Investigational and 83 Control).

STUDY POPULATIONS

ALL ENROLLED POPULATION

Subjects who have been randomized to the Investigational or Control group in this study comprise the All Enrolled population. The co-primary endpoints will be analyzed for the All Enrolled population and the results will be compared to the primary analyses performed on the Analysis population to determine whether the results of this analysis are consistent for both populations. For patients in the All Enrolled Population who are missing data necessary for the determination of any of the co-primary endpoints at 22+ months, data will be imputed as described below in the section “Sensitivity Analyses.”

ANALYSIS POPULATION

Subjects who have been randomized to the Investigational or Control group in this study and who have complete data for a primary endpoint collected per the protocol at 22+ months or who have had a revision or removal at or before 26 Months will be included in the Analysis Population. This is the population that will be used in the primary study analysis and determination of study success. Those subjects who are missing their primary endpoint at 22+ months will be included as part of the All Enrolled population described above. Subjects with protocol deviations will be analyzed on an individual basis to determine if they will be included in the Analysis Population.

MISSING DATA AND SENSITIVITY ANALYSES

Data will be considered “missing” for a given primary endpoint if this endpoint cannot be calculated or is not available for a subject in the All Enrolled population. If the subject has had a



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

device failure at any point on or prior to their 22+ month outcome, they will *not* be considered as missing data for the Absence of Revision/Removal/UAE endpoint, as this endpoint is cumulative. A subject who has had a revision or removal prior to two years will be considered a radiographic failure at the 22+ month time point for purposes of the primary analysis. When possible (i.e. the subject is seen by a study investigator in a non-emergency situation and collection of the data will not cause undue burden), ASES scores will be collected for these cases before the revision is performed in order to prevent these patients from missing knee scores in the primary efficacy analyses.

Sensitivity analyses will examine the sensitivity of the results to missing values of the primary outcomes using the following analyses:

<u>Outcome Type</u>	<u>Analysis Description</u>
Binary (Radiographic Success, Absence of Revision/Removal))	Tipping Point Analysis: Missing observations are replaced with values until the lower limit of the 95% Confidence interval for the difference in proportions is equal to the non-inferiority margin (the tipping point). Graph will show which imputations of success/failure for the missing values in the investigational and control groups lead to a conclusion of inferiority, and which lead to a conclusion of non-inferiority.
	Missing Values as Success: Imputation of missing values as “success”
	Missing Values as Failures: Imputation of missing values as “failure”
	Last Observation Carried Forward: Missing observations in either group are imputed by taking the most recent outcome prior to 24 months and using it in place of the missing 24-month outcome.
	2 Year In-Window Analysis : Only data collected within the 2-year per-protocol visit window (22-26 months) are included in this analysis.
	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.
Continuous (ASES Score)	Replace with Maximum: Imputation of missing ASES as “100”
	Replace with Minimum: Imputation of missing ASES as “0”
	Last Observation Carried Forward: Missing observations in either group are imputed by taking the most recent outcome prior to 24 months and using it in place of the missing 24-month outcome.
	2 Year In-Window Analysis : Only data collected within the 2-year per-protocol visit window (22-26 months) are included in



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

	this analysis.
	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.

In addition, in the event that one or more subjects receive the opposite treatment than the one they were randomized to receive, a sensitivity analysis will be done on patients “as randomized” to make sure it is consistent with the primary analysis (“as treated”). However, because randomization will be performed intra-operatively and the patient must be able to receive either treatment in order to be randomized, this situation is not expected to occur. Other sensitivity analyses will be conducted as needed (i.e. if the effect of missing data on a particular primary outcome is still unclear).

TESTS FOR INTERACTION

The association between the primary endpoints and device group at 22+ months across investigators will be examined using either an analysis of variance model (for ASES score) or the Breslow-Day test for homogeneity of odds ratios (for Radiographic Success and Absence of Revision/Removal/UADE). These tests for interaction will use a p-value of 0.10. If there is no evidence of treatment *center interaction ($p \geq 0.10$) for a particular outcome, data will be pooled across centers for that outcome. If $p < 0.10$, then this outcome for each site will be examined graphically to assess site dependency as well as whether or not a qualitative interaction exists. Further, the sites contributing to this interaction will be examined, and if necessary, a stratified analysis will be conducted and results compared to overall study results to assess consistency.

In addition, the association between device group and the primary endpoints for unilateral and bilateral subjects will be examined using either an analysis of variance model (ASES) or the Breslow-Day test for homogeneity of odds ratios (Radiographic Success and Absence of Revision/Removal/UADE). As before, a significant p-value ($p < 0.10$) for a particular outcome indicates heterogeneity in that outcome for unilateral and bilateral subjects; if this occurs, that outcome for each group will be examined graphically and descriptively to assess these differences. Primary outcomes for unilateral and bilateral subjects will also be compared using a Fisher’s exact test (Radiographic Success and Absence of Revision/Removal/UADE) or a pooled t-test (ASES). If $p < 0.10$ for the two-way comparison or the test for interaction, the



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

bilateral subjects will be compared as a separate group for that outcome, and additional unilateral subjects may be enrolled (via IDE supplement/protocol amendment) in order to protect statistical power of the primary study analysis.

PROTOCOL DEVIATIONS

A description of all protocol deviations will be provided. The association between the proportion of subjects with a protocol deviation and device group across investigators will be examined using the Breslow-Day test for homogeneity of odds ratios. Investigators with less than or equal to 3 cases in either treatment will be combined to form a “pooled” investigator for analysis. A significant p-value indicates heterogeneity of odds ratios for the proportion of subjects (Investigational vs Control) with a protocol deviation across investigators, and in this case the proportions of subjects with a deviation will be examined graphically and descriptively by treatment group and site to assess dependency.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

DATA COLLECTION

DATA COLLECTION TIME POINTS

Windows for this study will be as follows:

Table 1: Analysis Windows

Interval	Follow-Up Window (Days from Surgery)
Preoperative	≤ 0
6 Weeks	28-56
3 Months	78-106
1 Year	304-426
2 Year	669-791
2+ Year	> 791

The principal data collected is described in the following table:

Table 2: Principal Study Data

Study Parameter	Data Collected
Demographic and Baseline Measurements	Age, Height, Weight, Gender, Race/Ethnicity, Unilateral/Bilateral, Primary Diagnosis, Prior Treatments, Concomitant Medications
Efficacy Measurements	American Shoulder and Elbow Surgeons (ASES) Score, Constant Score, SANE Score, Radiographic Assessment
Safety Measurements	Revision/Removal, Adverse Events
Study Success Criteria	Study success requires that the Investigational group successfully demonstrate non-inferiority when compared to the Control group for all three of the individual primary endpoints.

INFERENCE METHODS

SIGNIFICANCE LEVELS

The Type I error rate for the primary study analysis will be 0.05.

Comparisons for secondary, exploratory, and safety analyses will use $\alpha = 0.05$, with no adjustment for multiple comparisons. Because no adjustments will be made for multiple



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

comparisons, secondary, exploratory, and safety endpoints will be reported as exploratory analyses without claims of statistical significance.

SUBJECT ACCOUNTING

Accountability tables will be generated to show, at each study visit, the number of Investigational and Control subjects who might be expected to attend a given visit and the number and proportion who did attend.

The following definitions specify how the subject accountability table tracks subject follow-up for the Control and Investigational arms:

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.

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

Revisions: The number of revisions that have taken place in the course of the investigational study recorded according to the scheduled follow-up visit.

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

Not Yet Overdue: Subjects in this category are those who have not yet been evaluated but who are still within the evaluation time window at the time of database closure.

Actual^A: The number of subjects with complete data (i.e. all primary outcomes 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 ("all evaluated" accounting).

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, or are not yet overdue in this time interval.

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

MODELS FOR CONTINUOUS MEASURES

Comparisons of Investigational vs Control with regard to continuous baseline and secondary outcomes will be performed using standard statistical tests and will be chosen as appropriate for the scale and distribution of the measures being analyzed. A t-test, Wilcoxon test, or one-way ANOVA (as appropriate) will be performed to assess differences.

CATEGORICAL DATA ANALYSES

Comparisons of Investigational vs Control with regard to categorical baseline, secondary and safety outcomes will be performed using standard statistical tests and will be chosen as appropriate for the scale and distribution of the measures being analyzed. Specifically, categorical outcomes will be compared for investigational and control groups using the Fisher's Exact test (for 2x2 tables) or the Likelihood Ratio chi-square test (for tables larger than 2x2).

BASELINE CHARACTERISTICS

Subjects in the Investigational and Control study groups will be compared regarding a list of baseline items, including preoperative ASES and Constant Scores, demographics (age, gender, and primary diagnosis), medical history, and comorbidities.

EFFICACY EVALUATIONS

Primary Endpoint

The confidence intervals used in the analysis of the binary primary endpoints (Radiographic Success and Absence of Revision/Removal/UADE) will be 1-sided, 95% confidence intervals for the difference between proportions in two independent samples. They will be calculated using the Wald method as based on a normal approximation to the binomial, as follows:

$$(p_C - p_I) + z_\alpha \sqrt{SE_C^2 + SE_I^2}$$

Where

p_C = proportion of success in the Control group,

p_I = proportion of success in the Investigational group,

$\alpha = 0.05$, and

$$SE_C = \sqrt{\frac{p_C(1-p_C)}{n_C}} \quad \text{and} \quad SE_I = \sqrt{\frac{p_I(1-p_I)}{n_I}}$$

The confidence interval used in the analysis of the continuous primary endpoint (ASES Score) will be a 95% confidence interval for the difference between means in two independent samples. They will be calculated using the normal distribution, as follows:

$$(\bar{x}_C - \bar{x}_I) + z_\alpha \sqrt{\frac{s_C^2}{n_C} + \frac{s_I^2}{n_I}}$$

Where

\bar{x}_C = mean ASES score in the Control group,

\bar{x}_I = mean ASES score in the Investigational group,

s_C = standard deviation of the ASES scores for the Control group,

s_I = standard deviation of the ASES scores for the Investigational group,

and

$\alpha = 0.05$

Secondary Endpoints

Secondary outcomes include the ASES score, SANE score, Constant score, and radiographic endpoints at 6 weeks, 6 months, 1 year, and 2 years separately. These outcomes will be compared for Investigational and Control groups at each time point.

Exploratory Analyses¹⁴

Subject covariates in the proposed statistical modeling below include treatment group, age at time of surgery, gender, BMI, primary diagnosis, and preoperative ASES score. Others may be added if other covariates potentially affecting the outcome become apparent. To determine the effect of these covariates on the primary endpoints, separate regression models will be used. In the regression models, the dependent variable will be the primary study endpoint; thus a logistic regression model will be needed for the binary study endpoints. The baseline and demographic variables listed above will be independent variables. A graphical examination of the residuals will be performed to assess the model assumptions. To determine whether a covariate has an effect on the primary study outcome, a Type 3 analysis of effects based on the Wald Chi-square test will be conducted.

In addition, the time to revision will be calculated for each subject in the investigative and control groups. For those individuals that do not experience a revision, their outcome will be classified as censored. Failure-free curves will summarize and illustrate the proportion of endpoint-free subjects for the Investigational and Control groups over the course of the study. The Kaplan-Meier product-limit method will be used to construct the endpoint-free curves for the Investigational and Control groups.

Also, a proportional hazards regression model will be fit to model the time-to-revision and censored data¹⁰. The principle time-to-revision model will include an independent variable for treatment group as well as baseline covariates that may have an effect on survival. The proportional hazards assumption will be assessed graphically and analytically. Once an adequate model has been fit, for the treatment effect and its standard error parameters will be

¹⁴ Exploratory Analyses described will be carried out if possible, depending on the data. If empty cells exist or models do not converge, these analyses will not be performed.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

estimated using partial likelihood. If there are a small number of tied event times, exact methods will be used to compute the likelihood; alternatively, Efron's approximation will be used¹¹.

The relationship between radiographic images and clinical outcomes will be evaluated by investigating how the primary clinical outcome, which is the change in ASES score from baseline to 22+ months, is affected by the primary radiographic outcomes, specifically the absence/presence of migration, the absence/presence of subsidence, radiolucencies, and osteolysis. This will be done using two-sample t-tests to compare the average change from baseline for patients with and without migration, and for patients with and without subsidence.

A comparison of the rate of reoperation for investigational vs control will be made using a Fisher's exact test.

SAFETY EVALUATIONS

ADVERSE EVENTS

All adverse events will be recorded, described, and compared for Investigational and Control groups. Adverse events resulting in device removal and/or revision will be collected and evaluated for differences across the control and investigational populations. Frequencies of adverse events, revisions/removals, and device related adverse events will be compared for investigational and control groups using the Likelihood Ratio chi-square test.

DATA COLLECTION, HANDLING AND RETENTION

SOURCE DOCUMENTATION REQUIREMENTS

Source documentation for this study will be maintained to document the treatment and study course of a subject and to substantiate the integrity of the trial data submitted for review to the regulatory agencies. Source documentation will include, but not be limited to, the paper or eCRF if data is directly entered there, study worksheets, hospital and/or clinic or office records documenting subject visits including study and other treatments or procedures, medical history and physical examination information, laboratory and special assessments results, device accountability records, and medical consultations. The investigator will make such records available for inspection by representatives of the sponsor, the IRB and the FDA, upon request.

CASE REPORT FORMS



Study of the Comprehensive® Shoulder System with nano Humeral Component in TSA: G110207

Data for this clinical trial will be collected and documented on the subject Case Report Forms (CRFs) provided which may be in paper form or in an electronic form. Authorized study site personnel will complete CRFs only.

Sample CRFs to be used with this clinical trial are provided in Exhibit 4.

STUDY DOCUMENT RETENTION

Study documents must be retained for a minimum of two years following completion of the study or longer as required in 21CFR Part 812.140.

DATA REPORTING

The sponsor is responsible for preparing annual reports of the study's progress. These reports will be submitted to the FDA and when approved, will be supplied to each site and their reporting IRB. A final report will also be prepared and disseminated in the same fashion.

Investigators are responsible for providing annual (or more frequent) reports as required by their IRB up to and including the final report at the study's completion.

ETHICAL AND REGULATORY REQUIREMENTS

CODE OF CONDUCT

The Investigator will ensure that the clinical study is conducted in accordance with

1. Protocol
2. FDA requirements (21 CFR Parts 812, 50 and 54).
3. IRB requirements

REGULATORY APPROVAL

This protocol must be approved by the FDA prior to study initiation.

INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEE

The Investigator must obtain appropriate Institutional Review Board (IRB) (or outside the United States, Ethics Committee (EC)) approval before the study can be initiated. A copy of the written approval from the IRB or EC and a copy of the approved informed consent form should be sent to the Sponsor.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Any changes to the protocol must be discussed and approved by the Sponsor in writing unless the change is made to assure the safety of the subject. Any change made emergently must be documented in the subject's medical record and the IRB or EC and the sponsor must be notified of the emergency change to the protocol within 5 days.

In the non-emergent setting, amendments to the protocol may only be implemented by the Sponsor. Approval from the IRB or EC must be received prior to initiation of the change. If applicable, approval from the FDA must also be obtained.

Other reports that are generated by the sponsor, including progress reports or safety reports must be provided to the IRB or EC. The investigator is also responsible for providing site progress reports as per the approving IRB or EC policies if applicable.

INFORMED CONSENT

Subjects (or the subject's legally authorized representative) will be provided with an informed consent form and given ample opportunity to review the consent and ask questions. The signed informed consent will be obtained before any study-specific procedures begin. If the subject agrees to participate in the study, the subject or his or her representative must sign the informed consent form. Other signatures should be obtained as required by the IRB or EC. A copy of the informed consent form should be given to the subject/representative. All subjects who meet all of the entry criteria will be considered for inclusion in this trial. Any subject meeting any of the exclusion criteria will be excluded from the trial.

The informed consent form must be documented on the most-current IRB-approved version of the form. Signed informed consent forms (or copies) are to be maintained in the study file and must be available for verification by monitors or inspectors.

A copy of the consent template is attached in Exhibit 5.

SUBJECT CONFIDENTIALITY

The sponsor will maintain the confidentiality of the identity of subjects enrolled in the study and the information contained in their study records to the extent possible. The Sponsor will also instruct the study investigators in the importance of maintaining the confidentiality of study



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

records. The records will be made available as required for review by governing regulatory agency such as FDA and a reviewing IRB, however to the extent possible; the subject's identity will not be disclosed.

SECTION C: RISK ANALYSIS

This investigation is designed to collect data on a new stemless humeral component used as part of a total shoulder system. The Comprehensive® Shoulder System with nano humeral component is intended to help the patient gain mobility and decrease pain. Risks associated with this shoulder system include general surgical and total shoulder arthroplasty risks. Due to the investigational nature of the system, there may be risks that are unknown. Other general medical problems associated with the patient's general medical health, including traumatic or motor vehicle accidents may occur and should not be suspected as being associated with the device unless that complication occurs in greater frequency in the investigational group than the control group.

GENERAL RISKS ASSOCIATED WITH SURGERY

As with any surgical procedure, there are risks involved with total joint replacement surgery.

Potential adverse events include, but are not limited to:

1. Complications resulting from anesthetic
2. Damage to nerves and blood vessels
3. Allergic reactions to the implanted devices
4. Phlebitis
5. Long-term swelling
6. Pulmonary embolus
7. Delayed wound healing
8. Prolonged illness
9. Hematoma
10. Wound dehiscence and/or drainage
11. Excessive bleeding that may result in the need for blood transfusions and/or further surgery
12. Permanent pain, deformity; and inconvenience.
13. Permanent brain damage
14. Pneumonia
15. Venous thrombosis
16. Heart attack
17. Kidney failure



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

GENERAL RISKS ASSOCIATED WITH TOTAL SHOULDER REPLACEMENT

1. Early or late infection perhaps necessitating device removal
2. Component dislocation and subluxation
3. Fracture or perforation of the bone (intraoperative or post operative)
4. Fracture, perforation, delamination (failure of the porous coating materials to adhere to the implant) of the device (intraoperative or post operative)
5. Device loosening or migration
6. Fretting or corrosion of implant interfaces
7. Wear and/or deformation of articulating surfaces
8. Particulate wear debris may initiate a cellular response leading to osteolysis
9. Damage to surrounding tissues, cartilage, or tendons
10. Inadequate range of motion
11. Persistent pain
12. Implantation of the device may require greater surgical exposure and prolonged surgical time
13. Instability
14. Periarticular calcification or ossification, with or without impediment of joint mobility
15. Undesirable shortening of limb
16. Disassociation of humeral head from humeral stem/component
17. Reoperations of the index shoulder to address post operative soft tissue pathologies (eg. Exploration of the brachial plexus, soft tissue release, long head of bicep pathology, rotator cuff tearing including subscapularis rupture/insufficiency, or soft tissue instability)

Rarely some adverse events may be fatal. These possible adverse events are not unique to the Comprehensive® Shoulder System with nano humeral component and, as stated above, may occur with any total joint replacement surgery.

Limitation may be imposed depending upon the patient's age, general health, baseline (pre-operative) activity level and baseline (pre-operative) condition of the shoulder and other joints.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

**POTENTIAL RISKS ASSOCIATED WITH COMPREHENSIVE® SHOULDER SYSTEM
WITH NANO HUMERAL COMPONENT IN TOTAL SHOULDER REPLACEMENT**

The safety and efficacy of the Comprehensive® Shoulder System with nano humeral component has not been demonstrated clinically, and patients participating in the study may be subject to increased risks and/or adverse events, in addition to those listed under general surgical risks, including, but not limited to:

- Failure of biologic fixation resulting in loosening or migration of the implant

Risks/Benefits from the Investigational Device

All of the risks associated with the use of the nano humeral component are the same as those described for a total shoulder replacement arthroplasty. Given the stemless design of the nano humeral component, there may be an increased level in some of the implant-related risks, particularly for failure of biologic fixation resulting in loosening or migration of the implant. Loosening or migration could affect the implant position resulting in an unsatisfactory surgical outcome. Additional surgery would be required to replace the implant with an alternate prosthesis if excessive loosening or migration of the nano humeral component occurs.

Use of the nano humeral component prosthesis may benefit patients by reducing the amount of bone removed during the surgical procedure. In addition the nano humeral component does not violate the canal of the humerus. The amount of retained native bone is greater than for stemmed shoulder prostheses and could facilitate surgery for replacement of the nano humeral component with a micro or mini stem. Traditionally if a standard sized stem needs to be revised or removed, a “long” stem is used to replace it which results in a further violation of the canal and removal of bone. Leaving the canal intact allows the shaft of the humerus greater flexibility in adjusting to forces applied to it.

MINIMIZATION OF RISK

With the increased understanding of failure modes for total shoulders, pre-clinical testing and clinical results found in the literature, it is believed that none of the previously mentioned adverse events will occur in significantly higher numbers compared to the control device. This investigational plan has reduced the potential risk to the patient through the following methods:



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

1. By defining a patient population that limits the exposure of the device to patients conforming to the proposed indications, exclusions, and age requirements
2. By utilizing surgeon investigators who are licensed orthopedic surgeons that have significant experience with primary total shoulder arthroplasty, thereby reducing surgical related risk.
3. Developing a surgical technique, including instrumentation specifically designed for the investigational device that may help eliminate potential operative difficulties

Prior to deciding whether to participate in the investigation, each subject will be provided with a description of all potential complications and increased risks. Patients will also be provided with a description of alternate treatments. With this information and the counsel of their physician, patients will decide whether participation in the investigation and potential use of the investigational device is in their best interest. The provision of this information and the patients' consent to participate in the investigation will be documented through the use of an Informed Subject Consent form.

Only licensed orthopedic surgeons who are practiced in total shoulder replacement surgical procedures will be allowed to participate as clinical investigators for this investigation. General surgical risks will be controlled by surgeon adherence to accepted surgical guidelines and procedures. Risks related to the prosthetic design will be controlled by device labeling, and the investigators' adherence to the instructions for its safe handling and use.

The sponsor will further minimize the identified and/or emergent risks throughout the investigation by requiring the clinical investigators to document and report all complications and adverse effects to the investigation sponsor. Any unanticipated adverse device events will be reported to each clinical investigator, reviewing Institutional Review Board (IRB) and to the FDA. Based upon an evaluation of such events, the sponsor may either amend the investigational plan or terminate the investigation to protect the rights, safety and welfare of the subjects. Should an IRB decide to suspend or withdraw its approval for a clinical investigator to conduct the investigation at that institution based on unacceptable risks to the investigational subjects, the investigation sponsor will notify all reviewing IRBs, clinical investigators and the FDA of this action. To further minimize risks, any new information obtained during the course



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

of the investigation relating to risks to the patient will be provided to subjects, investigators, and IRBs.

The investigation has been designed to minimize the number of patients exposed to the investigational device, yet provide sufficient numbers of subjects for valid scientific analysis of the compiled investigation data. The risks will be further controlled by the investigational design, the procedures for monitoring the dispensing of the investigational devices to the investigation subjects and the documentation, reporting, and evaluation of the results from its surgical use.

The potential risks to the subjects in this investigation have been further minimized by the preclinical and laboratory testing performed by the sponsor to verify the design requirements and the suitability for the intended use. Use of the investigational device is further supported by the reports from the medical and scientific literature for similar devices and the manufacturing processes and controls used to manufacture the prosthesis.

Description of Subject Population

Condition

As stated in the investigational plan, subjects must meet specific diagnostic and inclusion/exclusion criteria to be eligible for enrollment. Eligible subjects will be selected for recruitment into the investigation from the general population of patients presenting with non-inflammatory degenerative joint disease (NIDJD). Subject candidates at increased surgical risk due to specific existing medical conditions are excluded as stipulated in the investigational plan. The relevant medical history and overall condition of each subject will be recorded and evaluated in relation to the safety and efficacy of the investigational device. This will enable the sponsor to identify additional contraindications, adverse effects, existing conditions and concurrent treatments that may predispose the subject to increased risk for complications or device failure.

Number

A total of 132 investigational devices and 132 control devices will be entered, providing a total investigation size of 264 devices.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Age

Subjects younger than 21 years or older than 90 years of age at the time of surgery are excluded from the investigation. In accordance with general orthopaedic and total joint replacement guidelines, skeletally immature subject candidates will be excluded from investigation participation. Data concerning the age of each investigational subject will be collected and evaluated to identify any age-related contraindications, or complications associated with the investigational device.

Gender

There is no gender selection criteria prescribed for this investigation. Male and female subject candidates will be solicited for participation in the investigation without bias. The proportion of male to female subjects will be examined to assure that there is no difference between control and investigational groups with respect to this ratio. If an unexpected difference in this ratio exists between control and investigational groups, then a covariate analysis controlling for gender will be performed for the primary analysis of the investigation. This will assure that gender related effects, if they are present, do not bias investigation conclusions.

Conclusion

This clinical investigation will be conducted under a well-defined protocol and subjects will be informed of the potential risks, benefits, and alternate treatments available prior to giving their consent for participation as investigational subjects. Exposure to the investigational device will be determined at random. Subjects' clinical course will be closely monitored and reported on throughout the investigation and new information provided to them that could affect their willingness to participate. The investigation has been designed to expose the lowest possible number of subjects to the investigational device that will still allow for a valid, scientific analysis of the reported data. The reporting and assessment of all untoward events arising during the course of the investigation will also be required. Therefore, the sponsor believes that all risks that are reasonably foreseeable have been identified and the means for adequately controlling those risks described.

SECTION D: DEVICE DESCRIPTION**DEVICE DESIGN AND DESCRIPTION**

The Comprehensive® Shoulder System with nano humeral component is a humeral prosthesis system intended for use in shoulder replacement surgery. The implant can be utilized for primary shoulder replacement in conjunction with the 510(k) cleared Versa-Dial™ Humeral Heads (K040610, K060716) and Comprehensive® Hybrid Glenoids (K060694). A complete component listing is included in Exhibit 12.

INVESTIGATIONAL DEVICE DESCRIPTION

The subject of this clinical investigation is the Comprehensive® Shoulder System with nano humeral component, comprised of the following components:

- A porous-coated stemless humeral component for cementless fixation;
- A polished, modular (2-piece) humeral head for articulation with the glenoid component;
- A molded glenoid component with three peripheral pegs for cemented fixation;
- Regenerex central glenoid peg for cementless fixation

Humeral Components

- The stemless humeral component is manufactured from Ti6Al4V alloy. It consists of a central tapered region and six outer wings. The taper has a machine finish and accepts the taper adaptor of the humeral head component. A small groove is included just below the taper to accept an inserter/impactor. The bone-contacting outer surface features a porous coating of plasma-sprayed titanium alloy for cementless fixation in the proximal humerus. Six sizes are available – 30 mm, 32 mm, 34 mm, 36 mm, 38 mm, and 40 mm, as referenced to the outside diameter.
- The head component consists of two parts: a humeral head and a taper adaptor. The humeral head is manufactured from CoCrMo alloy, while the taper adaptor is made from Ti6Al4V alloy. The convex portion of the head is highly polished for smooth articulation against the glenoid component. The two



piece construct allows the offset to be adjusted from 0.5 mm to 4.5 mm and then oriented in any direction to maximize coverage of the resected humerus.

Glenoid Components

- The glenoid component consists of two parts: a glenoid base and a central peg.
- The glenoid base is manufactured from ultra-high molecular weight polyethylene. The base has three ribbed peripheral pegs that allow for cemented fixation in the glenoid.
- The central peg is manufactured from porous metal that is sintered over a solid Ti6Al4V alloy core. The porous metal of the central peg allows for cementless fixation of this portion of the glenoid component.

**CONTROL DEVICE DESCRIPTION**

The Comprehensive® Shoulder System with mini stem component, which will be the control device for this clinical investigation and was 510(k) cleared under K060692 on May 30, 2006, comprises the following components:

- Proximally porous-coated humeral stem for cementless fixation;
- Polished, modular (2-piece) humeral head for articulation with the glenoid component;
- Molded glenoid component with three peripheral pegs for cemented fixation;
- Regenerex central glenoid peg for cementless fixation

Humeral Component

- The humeral stem component is manufactured from Ti64AlV alloy. The taper has a machine finish and accepts the taper adaptor of the humeral head component. The proximal region of the bone-contacting outer surface features a porous coating of plasma-sprayed titanium alloy, while the distal portion is polished. Seventeen stem diameters are available – 4 mm to 20 mm, in 1-mm increments.
- The humeral head components are identical to those described in the Investigational Device Description section.





**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

Glenoid Components

- The glenoid component is identical to those described in the Investigational Device Description section.

SECTION E: MONITORING

The Investigator must allow regular inspection of all study records including CRFs, source documents and regulatory documents during the study by the monitor or other representatives of the sponsor. This measure is to ensure that the study is carried out and documented in accordance with federal regulations and the terms of this protocol. The Investigator also agrees to allow inspections by the FDA or their agents or other regulatory agencies before, during, or after the study has concluded, if such inspections are requested.

The monitor for this study will be the Clinical Operations Department of the Sponsor located at:
Biomet Manufacturing, Inc
56 E. Bell Dr.
Warsaw, IN 46581

Monitoring may also be conducted by consultants contracted by and acting on the behalf of the sponsor not known at this time. Regardless, monitoring will be conducted according to the most current version of the sponsor's business unit procedure and corporate procedure regarding monitoring. Samples of the sponsor's monitoring procedures are included in Exhibit 6.

SECTION F: LABELING

PACKAGE LABEL

Samples of the outer package label for the investigational Comprehensive® Shoulder System with nano humeral component are contained in Exhibit 7.

INSTRUCTIONS FOR USE (IFU)

A sample of the package insert (IFU) for the Comprehensive® Shoulder System with nano humeral component is contained in Exhibit 8.



Study of the Comprehensive® Shoulder System with nano Humeral Component in TSA: G110207

SURGICAL TECHNIQUE

The surgical technique for the Comprehensive® Shoulder System with nano humeral component is contained in Exhibit 9. A list of the instrumentation to be used for implantation of the investigational device is contained in Exhibit 10.

NOTE: A recommended rehabilitation protocol from Brigham and Women's Hospital has been provided in Exhibit 13. All patients are required to participate in a rehabilitation protocol as prescribed by their surgeon. Any patient that does not participate will be considered a protocol deviation.

SECTION G: CONSENT MATERIALS

A copy of the proposed informed consent for the study is contained in Exhibit 5.

SECTION H: IRB INFORMATION

Institutional Review Board information is provided after clinical research sites and investigators have been identified. Once sites have been identified for this study, the information will be sent to the Agency via the biannual Clinical Research site list update.

SECTION I: OTHER INSTITUTIONS

An independent radiographic reviewer will be utilized for assessment of radiographic variables. An independent adjudicator will be utilized for assessment of Adverse Event relationship to device and/or relationship to procedure.

SECTION J: ADDITIONAL RECORDS AND REPORTS

Copies of the Case Report Forms are contained in Exhibit 4.

REFERENCES

1. McCullagh, PJJ, Biomechanics and Design of Shoulder Arthroplasty, Proceedings of the Inst of Mech Engrs; Journal of Engineering in Medicine, vol 209, pp 207-213
2. Wirth, MA and Rockwood Jr., CA, Current Concepts Review – Complications of Total Shoulder-Replacement Arthroplasty, Journal of Bone and Joint Surgery-Am, 1996; 78: 603-16.
3. Bohsali K, Wirth M., Rockwood Jr. C. Complications of Total Shoulder Arthroplasty; J Bone Joint Surg Am 2006; 88: 2279-2292.
4. Radnay CS, Setter KJ, Chambers L et al. Total shoulder replacement compared with humeral head replacement for the treatment of primary glenohumeral osteoarthritis: a systematic review. J Shoulder Elbow Surg 2007; 16(4):396-402.
5. Boileau P, Walch G., The three-dimensional geometry of the proximal humerus. Implications for surgical technique and prosthetic design; J Bone Joint Surg Br 1997; 79(5): 857-65.
6. Norris, Tom et. al. "Functional outcome after shoulder arthroplasty for primary osteoarthritis: A multicenter study." Journal of Shoulder and Elbow Surgery. 2002; 11:130-135.
7. Dixon, W.J., Massey, F.J. Introduction to Statistical Analysis, 4th Edition. McGraw-Hill (1983) pp. 123-126.
8. O'Brien, R.G., Muller, K.E. Applied Analysis of Variance in Behavioral Science. Marcel Dekker, New York (1993) pp. 297-334.
9. Rubin, D.B. (1987), *Multiple Imputations for Nonresponse in Surveys*, New York: John Wiley & Sons, Inc.
10. Cox DR (1972) Regression models and life tables (with discussion). Journal of the Royal Statistical Society, Series B. vol. 34. pp. 187-220.
11. Effron B. The Efficiency of Cox's Likelihood Function for Censored Data. Journal of the American Statistical Association 1977; 72; 557-565.
12. The Brigham and Women's Hospital, Inc. Department of Rehabilitation Services. (2007). Total Shoulder Arthroplasty/Hemiarthroplasty Protocol, [PDF]. Available Protocol: http://www.brighamandwomens.org/Patients_Visitors/pcs/rehabilitationservices/Physical%20Therapy%20Standards%20of%20Care%20and%20Protocols/Shoulder%20-%20Total%20Shoulder%20Arthroplasty%20protocol.pdf [February 13, 2013].
13. Martin, et al. "Uncemented Glenoid Component in Total Shoulder Arthroplasty." *JBJS VOLUME 87-A · NUMBER 6 · JUNE 2005*.



**Study of the Comprehensive®
Shoulder System with nano
Humeral Component in TSA:
G110207**

EXHIBITS

Exhibit 1	Sponsor Procedure 48
Exhibit 2	Sponsor Procedure 52
Exhibit 3	Radiographic Protocol
Exhibit 4	Case Report Forms
Exhibit 5	Informed Consent Form
Exhibit 6	Monitoring Procedures
Exhibit 7	Sample Outer Package Label
Exhibit 8	Sample Package Insert
Exhibit 9	Surgical Technique
Exhibit 10	Instrumentation list
Exhibit 11	Study Logs
Exhibit 12	Component Listing
Exhibit 13	Recommended Post-Operative Rehabilitation Protocol