A PROSPECTIVE CONTROLLED MULTI-CENTER STUDY ON VANGUARD™ COMPLETE KNEE & VANGUARD™ HIGH FLEX RP KNEE

GENERAL INFORMATION

Principal Investigators

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Chul-Won Ha, M.D., Ph.D. – 75 Cases
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Principal investigators are responsible for the overall project and performing the surgical procedures in all study groups. Responsible for applying for ethical and management approval, recruitment of patients, obtaining patient consent, managing postoperative care of patients and adverse event reporting.

Study Sponsor

Biomet Korea

Study sponsors take responsibility for initiation, management, and/or financing of a clinical studies at investigational sites.

Study Monitor in Korea

Anna Lee

Study monitors are responsible for carrying out the monitoring procedure as indicated in the protocol.

STUDY OBJECTIVE

The primary objectives of this clinical study include:

- Evaluate size fit and long term performance of Vanguard Complete Knee ("Fixed") System in Asian and Latino population Compare Vanguard High Flex Rotating Platform ("High Flex") Knee System to Vanguard Complete Knee System in Asian population in terms of:
  - Early ROM
  - Clinical outcomes

- Compare current design to new design of Vanguard High Flex Rotating Platform Knee System in terms of :
  - Early ROM
  - Clinical outcomes

DEVICE DESCRIPTION

Vanguard Complete Knee

Vanguard Knee is a metal and polyethylene system designed to replace the body's natural knee joint and is indicated for cemented tibial and cementless femoral use. The system contains three (3) primary components and one (1) peripheral component. The primary components include, femoral, tibial, and bearing components, while the peripheral component is the patella button. The use of the patella button is optional.

Vanguard High Flex Rotating Platform Knee (current design)

Vanguard High Flex RP knee is an extension to the existing Vanguard Knee and has been specifically designed to facilitate greater than 135 degrees of knee flexion as required by certain patients. Specifically the Vanguard High-Flex Knee components are required to be able to flex to 150° without point loading or falling off the back of the tibia and to be hyper extended to 15°. It should be noted that this range of motion would only be obtained where the patient had similar flexion and hyperextension ability prior to the arthroplasty. The decision on which rotating platform variant to use is at the discretion of the operating surgeon

Mobile bearing knees are considered advantages as they enable improved congruency between the femoral component and the bearing, compared with a fixed bearing, which results in lower contact stresses of the bearing, thereby reducing wear. Another advantage of mobile bearings is the ability for self-alignment, which reduces wear caused by mal-lalignment, enabling the knee to function more naturally and prevents torsion stress on the implant/bone cement/bone interface which may cause loosening.

The tibial tray of the High Flex knee is available in 9 sizes, from 59 to 91mm in 4 mm increments, in interkok finish for cemented applications or with porous plasma sprayed titanium coating for cementless use. It is manufactured from cast cobalt chromium alloy. The stem has a tapered cone geometry for press fit stability. In the cementless option the proximal 1/3 of the stem is porous coated with plasma sprayed titanium. (Note: The tibial trays are manufactured and CE marked by Biomet Spain).

The femoral component is offered in thirteen sizes from 55 to 80mm in 2.5 mm increment, it is anatomic in design (i.e. right and left). It is manufactured from cast cobalt chromium alloy.

The bearing is compression moulded UHMPWE (ArCom). It is matched to the femoral component and is available in 5 thickness from 10-18mm (2mm increments) and 13 sizes from 50mm to 80mm (2.5mm increments). The bearing was designed specifically for the High-Flex to allow rotation of ±8° without overhang.

The patella has an anatomic design and is matched to the thirteen sizes of femoral component patella tracks. It is available in of one thickness only. It is compression moulded from UHMWPE (ArCom). Use of the patella button is optional at the discretion of the surgeon.

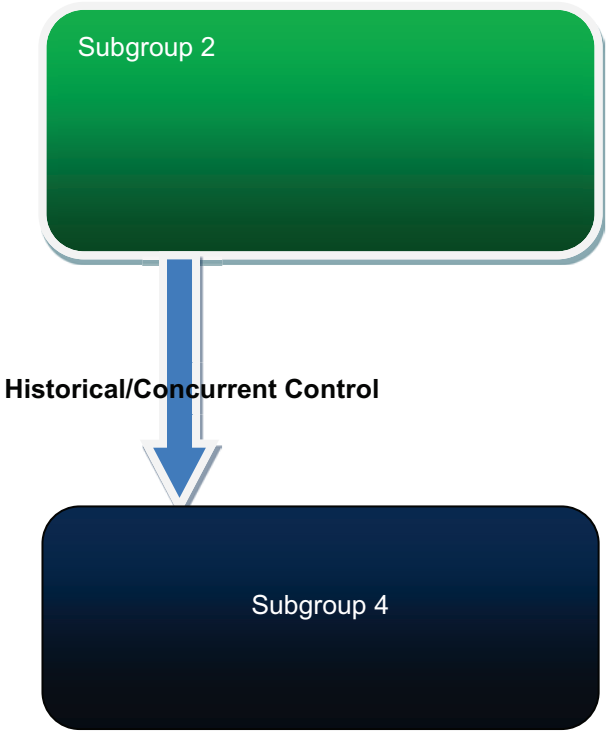
STUDY DESIGN

The study is designed as a prospective, controlled multi-center study including sites from Korea, Japan and Mexico.

To achieve all the primary objectives, the study will include 2 subgroups. The relationship between the two subgroups is illustrated in the following table and graph:

Subgroup	Objectives	Trial Group	Control Group	Design	Endpoint(s)
2	**Compare early ROM, Clinical Outcomes, assess Kinetic and Kinematic characteristics between Vanguard Complete Knee System and Vanguard High Flex Rotating Platform Knee System***	**Vanguard Complete Knee System w/ std tray (*part of subgroup 1 control*)**	**Vanguard High Flex RP (Current Design)**	**RCT**	**ROM, AKS,.**
4**	Compare early ROM, clinical outcomes and assess Kinetic and Kinematic characteristics between current design and new design of Vanguard High Flex Rotating Platform Knee Systems	Vanguard High Flex RP (New Design)	Vanguard High Flex RP *(same as control from subgroup 2)*	Historical/concurrent control	ROM, AKS, Survivorship and Fluoroscopic analysis, Gait lab analysis, patella clunk and crepitus.

**Japanese* sites *will include equal number of Healthy Knees for ROM, Kinetic and Kinematic analysis.*
*** Subgroup 4 will be initiated once the new design of Vanguard high flex RP is release.*



The study will be conducted over a period of 12 to 15 years. Patients from subgroups 2 and 4 will be followed at immediate postop, 6 weeks, 6 months, 1 year, 3 years, 5 years, 7 years and 10 years.

PATIENT SELECTION

All subjects, regardless of sex, race, or geographic location, must fit into the scope of the Inclusion / Exclusion criteria to be eligible for the study. If required per applicable regulations, all participants must sign an Informed Consent to be enrolled into the study.

Inclusion Criteria

In accordance with Indications for Use for Vanguard Complete Knee System and Vanguard High Flex Rotating Platform Knee System specifically:

- Painful and disabled knee joint resulting from osteoarthritis, rheumatoid arthritis, traumatic arthritis where one or more compartments are involved.
- Correction of varus, valgus, or posttraumatic deformity.
- Correction or revision of unsuccessful osteotomy, or arthrodesis.

Patient selection factors to be considered also include:

- Need to obtain pain relief and improve function

- Ability and willingness of the patient to follow instructions, including control of weight and activity level
- A good nutritional state of the patient, and
- The patient must have reached full skeletal maturity

Exclusion Criteria

In accordance with Absolute and Relative Contraindications for use for Vanguard Complete Knee System and Vanguard High Flex Rotating Platform Knee System.

Absolute contraindications include: infection, sepsis, osteomyelitis, and failure of a previous joint replacement.

Relative contraindications include:

A. Uncooperative patient or patient with neurologic disorders who are incapable of following directions,
B. Osteoporosis,
C. Metabolic disorders which may impair bone formation,
D. Osteomalacia,
E. Distant foci of infections which may spread to the implant site,
F. Rapid joint destruction, marked bone loss or bone resorption apparent on roentgenogram,
G. Vascular insufficiency, muscular atrophy, neuromuscular disease,
H. Incomplete or deficient soft tissue surrounding the knee.

ENDPOINTS

	SUBGROUP 2	SUBGROUP 4
PRIMARY ENDPOINTS*	Range of Motion at 1 yr postop. AKS at 1 year postop	Range of Motion at 1 yr postop. AKS at 1 year post op
SECONDARY ENDPOINTS	At all follow-up visits: Survivorship American Knee Society Score. Range of Motion Radiographic Assessment Patient Satisfaction – EQ5D Complications including revisions Patella Clunk and Crepitus	At all follow-up visits: Survivorship American Knee Society Score. Range of Motion Radiographic Assessment Patient Satisfaction – EQ5D - OKS - FJS Complications including revisions Patella Clunk and Crepitus

*For sample size calculations.

PARTICIPANT POPULATION (SAMPLE SIZE)

Participant population is determined based on primary/secondary endpoints of each subgroup following superiority or non-inferiority methodologies. Minimum sample sizes are determined in order to prove the hypotheses.

Subgroup 2 - Primary Endpoint Range of Motion at 1 year postoperative

Superiority test

Null Hypothesis: H_0 $\mu_t = \mu_c$

Alternative Hypothesis: H_a $\mu_t = \mu_c + d$

μ_t: mean of ROM in the trial group (Vanguard Complete Knee) at 1year postoperative.

μ_c: mean of ROM in the control group (VG RP Knee) at 1 year postoperative.

a = 0.025 Significance Level (95% confidence)

β = 0.20 80% Power

d = 5 (degrees) Clinically Relevant Difference in ROM based on literature and engineering input.

ξ = 17.5 Estimate standard deviation of ROM at 1 year postoperative. This value is based on results (preop and 1 year postop) from literature[1]

N = 231

Consider lost to follow-up at 1 year postop, therefore the adjusted sample size is set *as **250 knees*** **per group (a total of 500 knees).**

Subgroup 2 - Secondary Endpoint AKS at 1 year postoperative

Non-inferiority test

Null Hypothesis: H_0 $\mu_t = \mu_c$

Alternative Hypothesis: H_a $\mu_t = \mu_c + d$

μ_t: mean of AKS score in the trial group (Vanguard Complete Knee) at 1 year postoperative.

μ_c: mean of AKS score the control group (VG RP Knee) at 1 year postoperative.

[1] Miner AL, Lingard EA, Wright EA, Sledge CB, Katz JN; Knee range of motion after total knee arthroplasty: how important is this as an outcome measure, J Arthroplasty. 2003 Apr;18(3):286-94.

a = 0.025 Significance Level (95% confidence)

β = 0.10 80% Power

$Z_{1-a/2}$ = 1.96
$Z_{1-\beta}$ = 1.28

d = 10 points Clinically Relevant Difference in Pain.

ξ = 15 Estimate standard deviation of AKS at 1 year postoperative. This value has been based on results from Biomet studies

N = 48
Consider possible lost to follow-up at 1 year postop, therefore the adjusted sample size is set as 51 knees per group. The final sample size for subgroup 2 is larger of the two sample sizes: 250 knees per group.

Therefore there will be 250 Vanguard Complete Knee will be compared to 250 Vanguard High Flex RP knee for subgroup 2 study.
Due to unknown release schedule for new designed VG High Flex RP Knee, sample size of subgroup 4 will be determined at time of the product release. Nevertheless the sample size will be determined based on the comparison to results of 250 VG High Flex RP knee of current design from subgroup 2.

RANDOMIZATION

For subgroup 2 study, patients will be randomized to receive Vanguard Complete Knee (trial group), or Vanguard High Flex RP Knee (control group). Patients have an equal opportunity of being assigned to the trial group or control group. The randomization will occur via a random number generator (manual or computer). The doctor or other health care professional does not choose the participants for each group. For Patients satisfying inclusion criteria, randomization will occur by retrieving the next randomly generated group assignment.

INSTITUTIONS

There will be a maximum of 8 sites from Korea and Japan in subgroup 2. The number of sites for subgroup 4 will be determined once new design of Vanguard High Flex RP is released.

PARTICIPANT DATA MANAGEMENT

The following table summarizes data collection required during the course of the study.

SUBGROUP 2	PRE-OP	SURGERY	IMMEDIATE POST-OP	3 MO	6 MO	1 YR	3 YR	5 YR	7 YR	10 YR
Informed Consent	X									
Demographic	X									

and Historical Record										
Preoperative AKS	X									
Operative Record		X								
Immediate Post-Operative Radiographic Assessment (Bench Mark)			X							
Postoperative AKS (Including ROM)				X	X	X	X	X	X	X
Patella Clunk and Crepitus				X	X	X				
EQ5D				X	X	X	X	X	X	X
Radiographic Assessment				X	X	X	X	X	X	X
Complications & Revisions				**Anytime**						

SUBGROUP 4	PRE-OP	SURGERY	IMMEDIATE POST-OP	3 MO	6 MO	1 YR	3 YR	5 YR	7 YR	10 YR
Informed Consent	X									
Demographic and Historical Record	X									
Preoperative AKS	X									
Operative Record		X								
Immediate Post-Operative Radiographic Assessment (Bench Mark)			X							
Postoperative AKS (Including ROM)				X	X	X	X	X	X	X
Patella Clunk and Crepitus				X	X	X	X	X	X	X
EQ5D/SF36				X	X	X	X	X	X	X
Radiographic Assessment				X	X	X	X	X	X	X
Complications & Revisions				**Anytime**						

PARTICIPANT EVALUATION SCHEDULES

All study Participants are expected to return for clinical, kinetic and kinematic analysis if any and radiographic evaluation at specific follow-up intervals. The following table summarizes the schedule for post-operative follow-up time intervals:

Evaluation Schedule		
Interval	**Follow-Up Window**	**Months Post-Op Range**
Immediate Post-Op	± 2 weeks	Immediate post-op < 2 weeks
3 month follow-up	± 1 month	2-4
6 month follow-up	± 1 month	5-7
1 year follow-up	± 2 months	10-14
3 year follow-up	± 3 months	33-39
5 year follow-up	± 3 months	57-63
7 year follow-up	± 3 months	81-87
10 year follow-up	± 3 months	117 - 123

COMPLICATIONS (ADVERSE EVENTS)

All adverse events, device related (*see Risk Analysis Section)* or non-device related, are to be recorded. Anticipated adverse events are defined, but not limited to, the following:

- Operative side knee manipulations or injections
- Operative side dislocations
- Operative side aspiration of joint fluids
- Falls
- Accidents- motor vehicle, motorcycle, ATV, etc.
- Death
- Any event in which the subject requires hospitalization or outpatient medical attention, including but not limited to: myocardial infarction, cerebral vascular accident, pulmonary emboli, gastrointestinal disorders, or a new diagnosis of a chronic condition (lung disease, renal disease, cancer, diabetes mellitus, hematological abnormalities, etc.).

RADIOGRAPHIC PROTOCOL

1. Radiographic Views
   The study requires a standard anteroposterior view, mediolateral view, and a skyline patellar view.

2. Reviewer
   The study investigator will assess his own patient's radiographs.

3. Assessment Procedure
    - Assessments will be recorded on the following two radiographic assessment reports:
        - Form XR100 (immediate post-operative)
        - Form XR200 (6 week, 6 month, 1 year, 3 year, 5 year, 7year and 10 year.
    - The radiographic films will be marked for measurements as described in the following "Measurement angles and reference points" section of this document. These "marked" radiographs will be used to determine the implant femoral flexion angle (α), tibial angle (β), total valgus angle (Ω), tibial angle (σ), and femoral flexion (γ).
    - The immediate post-operative film will be used as an index for subsequent follow-up assessments.

    The radiographic assessment definitions are as follows:
    - Anteroposterior Radiograph:
      This radiographic view can be obtained with the participant in the standing or recumbent position.
    - Mediolateral Radiograph:
      This radiographic view can be obtained with the participant in the standing or recumbent position.
    - Skyline Radiograph:
      This radiograph view can be obtained with the patello-femoral joint in flexion
    - Radiolucency or Radiolucent Lines:
      A radiographic clearing or line not exceeding 2mm in width at the bone/cement or cement/implant interface
    - Osteolysis:
      A progressive radiolucency > 2mm in ***two or more*** zones not present on immediate postoperative radiographs and/or a bony destructive lesion that is progressive in nature.
    - Migration/Subsidence:
      A component migration of > 3 mm or > 3° as compared to immediate post-operative radiographs is considered a failure.

DATA COLLECTION

All sites will be required to complete and submit case report forms on Biomet's online database, Joint Assist 2.0, in a timely manner. Forms will be monitored for completeness and accuracy.

Further, it is imperative that the investigator answers all questions on the case report forms. All data should be accurate, indelible, legible, dated on the date of entry, and signed by initials, and/or formal signature by the authorized personnel documenting the data.

MONITORING PLAN

Prior to commencing the study the Monitor will provide the investigators with the necessary information to enable him/her to carry out his responsibilities. This information includes but not limited to:

- Investigator Brochure i.e. study protocol, investigator responsibilities, device information, etc.

- Ethical Committee Approval Information.
- Case Report Forms.
- Patient Consent Forms
- EDC user manual

The monitor of the evaluation periodically reviews the post-operative follow-up dates on all subjects for each evaluator. A follow-up schedule is then sent to each investigator, which illustrates any follow-up, reports which are due or missing. Every effort is made to assure that follow-up reports are completed in a timely manner, including contacting the evaluator by post, telephone or by personal visit when necessary. Also, during the course of the evaluation, the monitor will conduct periodic discussions with the investigator or staff to ensure that the evaluation is being conducted in accordance with the protocol. The monitor will maintain records of each visit or discussion.

CONFIDENTIALITY

To ensure study patients' privacy, all patients will be identified by unique identification numbers. All case report forms will only include patient IDs. It is the responsibility of the investigator to maintain a list of patient identification and Joint Assist 2.0 ID numbers.

Further the Joint Assist database is restricted, allowing a doctor to only view and enter data from his own patients. User authentication is required to view research data. The data is transmitted to a centralized database through a secured (SSL) channel on the Internet. Data in transit is in 128-bit encryption. The access to the centralized database is limited to those who are responsible for maintaining the database.

RISK ANALYSIS

This clinical study is to collect data on the Vanguard DD RP Knee, which is intended to help the participant gain mobility and decrease pain. Risks associated with this knee system include general surgical and knee arthroplasty risks. Due to the investigational nature of the system, there are unknown risks.

General Surgical Risks

As with any surgical procedure, there are risks involved with total joint replacement surgery. Potential adverse events include, but are not limited to: early or late infection perhaps necessitating device removal; component dislocation; damage to nerves and blood vessels; fracture of the bone or device; device loosening; allergic reactions to the metallic devices; phlebitis; long-term swelling; pulmonary embolization; and delayed wound healing. Other potential adverse effects include: prolonged illness; hematoma; wound dehiscence and/or drainage; the need for blood transfusions and/or further surgery; or permanent pain; deformity; and inconvenience. Risks associated with the anesthetic are those such as permanent brain damage, pneumonia, blood clots, and heart attack. Rarely some adverse events may be fatal. These possible adverse events are not unique to the Vanguard™ RP System and, as stated above, may occur with any total joint replacement surgery.

As with any joint replacement post-operative activity, limitations may be imposed

depending upon the participant's age, general health, baseline (pre-operative) activity level and baseline (pre-operative) condition of the knee and other joints.

Potential Risks Associated with Vanguard™ RP Knee System

The safety and efficacy of the Vanguard™ RP Knee System has not been thoroughly demonstrated clinically, participants participating in the study may be subject to increased risks and/or adverse events including, but not limited to:

1. Material sensitivity reactions
2. Early or late post-operative infection and/or allergic reaction
3. Intra-operative bone perforation or fracture
4. Loosening or migration of implants
5. Periarticular calcification or ossification, with or without impediment of joint mobility
6. Inadequate range of motion
7. Dislocation or subluxation of device
8. Fatigue fracture of components
9. Fretting or corrosion of implant interfaces
10. Wear and/or deformation of articulating surfaces
11. Valgus/Varus deformity
12. Transient peroneal palsy secondary to surgical manipulation and increased joint movement
13. Patellar tendon rupture and ligamentous laxity
14. Intra-operative or post operative bone fracture
15. Post operative pain and/or delayed wound healing
16. Inadequate lubrication
17. Implant of the device may require a more demanding implantation procedure with greater surgical exposure and prolonged surgical time
18. Damage to surrounding tissues, cartilage, or tendons
19. Long term swelling
20. Excessive bleeding
21. Instability

Minimization of Risk

With the increased understanding of failure modes for mobile bearing knees, pre-clinical testing and clinical results found in the literature, it is believed that none of the previously mentioned adverse events will occur in significant numbers. This investigational plan has reduced the potential risk to the participant through the following methods:

1. By defining a participant population that limits the exposure of the device to participants conforming to the proposed indications, exclusions, and age requirements
2. The surgical technique has been developed to help eliminate potential operative difficulties.

REFERENCES

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