Simplex HV Bone Cement

CLINICAL PROTOCOL

A Retrospective Multicenter Study to Review the Use of Simplex High Viscosity Bone Cement in Primary Total Knee Arthroplasty

Sponsor:	*Stryker Orthopaedics* *325 Corporate Drive* *Mahwah, NJ 07430* *201-831-5000*
EU legal representative:	*Stryker European Operations Ltd* *IDA Business Park Anngrove* *Carrigtwohill, Co. Cork* *Ireland*
Study Product:	*Bone Cement:* *Simplex® HV* *Simplex® HV with Gentamicin*
Protocol Number:	*80*
510(k) Clearance Number:	K123225 Simplex HV K123081 Simplex HV with Gentamicin
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CONFIDENTIAL

Protocol Change History

Version	Description	Justification for change	Changed By
A	New		
1.0	Final	NA	

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List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
BMI	Body Mass Index
CRA	Clinical Research Associate
CRF	Case Report Form
CSM	Clinical Study Manager
DCR	Data Clarification Request
EC	Ethics Committee
HV	High Viscosity
IRB	Institutional Review Board
KSS	Knee Society Score
OKS	Oxford Knee Score
PROMs	Patient Reported Outcome Measures
QoL	Quality of Life
ROM	Range of Motion
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Study Coordinator
TKA	Total Knee Arthroplasty
UADE	Unanticipated Adverse Device Effect

Study Synopsis

Title	A Retrospective Multicenter Study to Review the Use of Simplex High Viscosity Bone Cement in Primary Total Knee Arthroplasty
Short Title	Simplex HV
Protocol Number	80
Phase	Post Market
Methodology	International, multicenter, retrospective follow-up of a consecutive series of patients
Study Duration	Examination of retrospective patient data from a determined period of 24 months, optional 5 years including pre-operative and intra-operative assessment
Number of Centers	2-5
Objectives	Primary: To evaluate the success rate of cemented Triathlon Total Knee components implanted using Simplex high viscosity bone cement (Simplex HV). Success is defined as absence of revision due to aseptic loosening in cemented Triathlon Total Knee components implanted with Simplex HV at 24 months. Secondary: To review OKS, KSS results and complications of patients who have received Simplex HV in a Triathlon Total Knee Arthroplasty.
Number of Cases	A minimum of 100 Simplex HV cases and 100 Simplex HV-Gentamicin cases who have received cemented Triathlon Total Knee System will be enrolled.
Inclusion/Exclusion Criteria	Inclusion Criteria: A. The Patient is age 18 or over at time of study device implantation B. Patients who have undergone primary Triathlon Total Knee Arthroplasty in which Simplex HV/Simplex HV Gentamicin was indicated for fixation and used on label C. Patients who have been followed for at least 24 months postoperatively Exclusion Criteria: A. Patients who have undergone revision surgery B. Patients who have undergone bilateral Knee Arthroplasty C. Patients contraindicated for either the devices implanted, or the cement used, according to medical history review and instructions for use D. Patient has a cementless tibial baseplate. E. Patient has an active or suspected latent infection in or about the affected knee joint F. Patient has muscle loss or neuromuscular impairment in the affected limb that would create an unjustifiable risk

	G. Patient is immunologically suppressed or receiving steroids in excess of normal physiological requirements (e.g. > 30 days) H. Patient has a known hypersensitivity to any of the cements constituents or in patients with severe renal failure I. Patient is a prisoner
Study Device	Bone Cement: • Simplex® HV • Simplex® HV with Gentamicin
Statistical Methodology	• No sample size calculation because a number of 100 cases per study arm was pre-defined by the regulatory body. • The success rate at two years will be presented with 95% confidence interval. • Frequency and percentage will be presented in tabular form for categorical variables. The mean, standard deviation, minimum and maximum values will be presented for quantitative variables.

Evaluation Schedule

Evaluation	Pre-operative	Intra-operative	24 (+2) months post-operative	27 months up to 5 years post-operative
Inclusion/Exclusion	x			
Demographics & Medical History	x			
KSS	x		x	optional
Surgical Details		x		
Implant and Cement Details		x		
OKS	x		x	optional
A/P and Lateral X-ray Interface			x	optional
Adverse Events		x	x	per protocol

Table 1 Evaluation Schedule

1 Introduction

This document is a protocol for a retrospective human research study. This study will be conducted in compliance with the protocol, international standard ISO 14155 Standards, associated Federal regulations and all applicable research requirements.

1.1 Background

The American Joint Replacement Registry (AJRR) shows an annual increase from approximately 20,000 to almost 130,000 in primary TKAs from 2012 to 2017. In the same time the use of High Viscosity Cement (HVC) in primary knee arthroplasty increased steadily from 46% to 61%[1].

Most of commercially available acrylic bone cements are based upon polymethylmethacrylate (PMMA) and methylmethacrylate (MMA) systems and consist of powdered and liquid components[2]. The polymerization of bone cement occurs through a progression of 4 phases: mixing phase, waiting phase, working phase, and hardening phase. HVC has some advantages over low-viscosity cement (LVC) including shorter mixing and waiting phases, whereas the working and hardening phases are longer. Operational efficiencies are receiving greater interest by surgeons and hospital administrations because high viscosity (HV) bone cements provide a shorter dough time than medium viscosity cements, which may result in surgical efficiencies by

allowing surgeons to handle and apply the cement to implant components and bone earlier while having more time to work with the cement during implantation of the components.[1,2,3].

The most common reason for failure of TKA is infection followed by implant loosening, polyethylene wear, and instability[4]. With the use of HVC, the literature describes a focus on aseptic loosening of the tibial component probably resulting from debonding of the cement-tray interface[3,4]. Considering the exact cause may be unknown, some authors suggest associations of this type of failure to the use of high-viscosity cement [5,6]. In contrast, a retrospective review of 1851 cases of primary TKA (obese patients with BMI >35) using HVC mixed with Gentamicin showed one revision due to aseptic loosening[3].

This study is a retrospective investigation of subjects who have received primary Triathlon Total Knee Arthroplasty inserted with Simplex High Viscosity (HV) Cement to evaluate the success rate defined as absence of revision for aseptic loosening of components at two years postoperative.

1.2 Clinical Data to Date

This study is the first Stryker Joint Replacement sponsored retrospective data collection on the Simplex HV bone cement.

2 Clinical Study Plan

2.1 Study Design

A retrospective, post-market, multi-center design will be employed.

2.2 Study Centers

Cases will be enrolled retrospectively at two to five centers which will enroll a minimum of 100 cases with Simplex HV non-medicated and 100 cases with Simplex HV with Gentamicin. All participating centers will comply with the federal regulations and apply at the responsible Institutional Review Board (IRB) or Ethics Committee (EC) for patient informed consent waiver. Non-compliance of a study center may result in termination of the center's participation in the study.

2.3 Number of Subjects

Cases will be enrolled until a total of 100 cases with Simplex HV non-medicated and 100 cases with Simplex HV with Gentamicin were observed and collected. Depending on the hospital

standard of care, a site may only enroll subjects receiving Simplex HV non-medicated and another site may only enroll subjects receiving Simplex HV with Gentamicin.

3 Device Description

3.1 Study Device

Simplex HV is available non-medicated and medicated with Gentamicin antibiotic.

The US listing number are Simplex HV: D295829 and Simplex HV with Gentamicin: D295830.

The Simplex HV bone cement is FDA recognized and registered under D-U-N-S-Number 344261631[1].

Simplex HV with Gentamicin is registered in the Australian Register of Therapeutic Goods (ARTG) under 276417.

Simplex HV/Gentamicin is CE certified under 135-0581-01 and Simplex HV under 135-0595-01.

3.1.1 Simplex HV Non-medicated Orthopaedic Cement

Simplex HV bone cement is a fast-setting acrylic resin for use in bone surgery. Mixing the two separate sterile components produces a ductile bone cement which, after hardening, fixes the implant and transfers stresses produced during movement evenly to the bone. Simplex HV cement powder also contains insoluble zirconium dioxide as an X-ray contrast medium. Simplex HV does not emit a signal and does not pose a safety risk in a magnetic resonance environment. Simplex HV is a substance designed to be used in arthroplastic and/or osteosynthetic procedures for the fixation of polymer or metallic implants to the living bone. It is typically made from methylmethacrylate, polymethylmethacrylate (PMMA)[2], esters of methacrylic acid or copolymers containing polymethylmethacrylate and polystyrene. This device does not contain an antimicrobial agent. The option for high viscosity does not compromise depth of intrusion. After application, this device cannot be reused.

Composition of cement powder:	40g	**Composition of liquid:**	20ml
Poly (methylacrylate/methylmethacrylate)	33.7 g	Methylmethacrylate (stabilized with 60 ppm HQ)	18.4 g
Zirconium dioxide	6 g	N,N-dimethyl-p-toluidine	0.4 g
Benzoyl peroxide	0.3 g		

Table 2 Simplex HV non-medicated component composition

[1]The FDA formally recognized the D-U-N-S-Number as an acceptable unique facility identifier (UFI) for the Foreign Supplier Verification Programs (FSVP). The identification of importers will help the FDA effectively implement, monitor compliance with, and enforce the FSVP requirements.

[2] Simplex HV bone cement contains 40g polymethyl methacrylate (PMMA) powder and 20 ml methylmethacrylate (MMA) liquid.

In partial or total replacement of the hip, knee and other joints, Simplex HV is indicated for fixation of synthetic resin polymer and metal prosthesis components in uninfected vital bones if joint reconstruction is required. In tumour surgery, Simplex HV is used in combination with internal fixation to fill bone cavities after tumour removal.

The use of Simplex HV is contraindicated if muscle wasting or neuromuscular compromise in the affected limb renders the procedure unjustifiable. Simplex HV should not be used in the event of known hypersensitivity to any of its constituents or if there are active or inadequately treated infections in the region of the implant.

3.1.2 Simplex HV with Gentamicin

Simplex HV bone cement with Gentamicin is a fast-setting acrylic resin with addition of Gentamicin sulfate for use in bone surgery. The added antibiotic, Gentamicin sulfate, protects the implant and the surrounding tissue from colonization with pathogens that are sensitive to gentamicin. Simplex HV with Gentamicin cement powder also contains insoluble zirconiumdioxide as an X-ray contrast medium. Simplex HV with Gentamicin does not emit a signal and does not pose a safety risk in a magnetic resonance environment.

Mixing the two separate sterile components produces a ductile bone cement which after hardening, fixes the implant and transfers stresses produced during movement evenly to the bone.

Composition of cement powder:	40.8 g	**Composition of liquid:**	20ml
Poly (methylacrylate/methylmethacrylate)	33.7 g	Methylmethacrylate (stabilized with 60 ppm HQ)	18.4 g
Zirconium dioxide	6 g	N,N-dimethyl-p-toluidine	0.4 g
Benzoyl peroxide	0.3 g		
Gentamicin base (added as Gentamicin sulfate)	0.5 g (0.8 g)		

Table 3 Simplex HV Gentamicin component composition

Simplex HV with Gentamicin is indicated for fixation of synthetic resin and metal prosthesis components during partial or total replacement of the hip and knee as well as other joints, if an infection with organisms that are sensitive to gentamicin is diagnosed or suspected. The antibiotic provides protection against bacterial colonization of the implant and the surrounding tissue.

Simplex HV with Gentamicin can be used for filling and stabilizing bone defects within the scope of internal fixation treatment, if there is an increased risk of infection with pathogens that are sensitive to gentamicin.

The use of Simplex HV with Gentamicin is contraindicated, if muscle wasting or neuromuscular

compromise in the affected limb renders the procedure unjustifiable. Simplex HV with Gentamicin should not be used in the event of known hypersensitivity to any of its constituents or in patients with severe renal failure.

3.2 Ancillary Devices

Additionally, only the following **Stryker Orthopaedics compatible** ancillary devices may be used, according to this study protocol:

- Triathlon Total Knee System

4 Study Procedures

4.1 Subject Recruitment and Screening

Subjects will be enrolled at the study centers using the electronic medical record, paper charts, information from pre- and postoperative images, intraoperative notes, and follow-up data collected as part of the hospital's routine care. The eligibility of these subjects will be assessed, according to the inclusion/ exclusion criteria.

All personal identifiable patient information will be pseudonymized and tracked via a unique subject number, known only to the site. Data extracted from the subject hospital files (paper or electronically stored); will be entered into paper case report forms (CRF).

4.2 Patient Informed Consent and Guidelines

The study protocol will be submitted for IRB/ EC Review. As pseudonymized retrospective patient data will be used, a requirement for informed consent is not expected, however waiver of consent from the IRB/EC is required.

5 Study Details

5.1 Inclusion/Exclusion Criteria

Inclusion Criteria:

A. The Patient is age 18 or over at time of study device implantation
B. Patients who have undergone primary Triathlon Total Knee Arthroplasty in which Simplex HV/Simplex HV Gentamicin was indicated for fixation and used on label
C. Patients who have been followed for at least 24 months postoperatively

Exclusion Criteria:

A. Patients who have undergone revision surgery
B. Patients who have undergone bilateral Knee Arthroplasty
C. Patients contraindicated for either the devices implanted, or the cement used, according to medical history review and instructions for use
D. Patient has a cementless tibial baseplate.
E. Patient has an active or suspected latent infection in or about the affected knee joint
F. Patient has muscle loss or neuromuscular impairment in the affected limb that would create an unjustifiable risk
G. Patient is immunologically suppressed or receiving steroids in excess of normal physiological requirements (e.g. > 30 days)
H. Patient has a known hypersensitivity to any of the cements constituents or in patients with severe renal failure
I. Patient is a prisoner

5.2 Pre-operative Data Collection

- Patient demographics
- Diagnosis/reason for the primary total knee arthroplasty, operative side
- Preoperative medical history: Relevant concurrent medical condition and treatment
- Knee Society Score (KSS)
- Oxford Knee Score

5.3 Intra-operative Data Collection

- Surgical details
    - Type of anesthesia
    - Anesthesia class ASA
    - Systemic prophylactic therapy
    - Surgical approach
    - Surgeon initials
    - Skin to skin and tourniquet time
    - Blood loss
- Simplex HV details
    - Cement storing temperature
    - Operating room temperature
    - Cement type

  - Cement use
  - Cement preparation
- Triathlon Total Knee Replacement details
  - Femoral component
  - Tibial component
- Intra-operative Adverse event or device deficiency

5.4 Post-operative Data Collection

Data collection at 24 months (+ 2 months) postoperatively and optional at 5 years postoperative.

- Knee Society Score (KSS)
- Oxford Knee Score (OKS)
- X-ray collection for independent analysis
  - A/P view
  - Lateral view
- Elective surgery since study surgery
- Post-operative Adverse event or device deficiency

6 Adverse Events

6.1 Reporting of Adverse Events

The AE reporting requirements for this study are as follows:

- All AEs that meet the definition of serious
- All AEs related to the operative site, regardless of seriousness or time of occurrence

On retrospective review of postoperative data, investigators and study coordinators (SCs) will search the subject's hospital files as to whether they have seen a doctor for any reason, been hospitalized for any reason or have a current impediment to their function.

If it is determined upon this further investigation that a protocol-defined AE has occurred, the SC will be responsible to complete an AE CRF. If the event is related or uncertain related to the Triathlon TKA or to Simplex HV, the investigator will verify if the event has been reported to Stryker at time point of occurrence or will report at time point of data review at the latest. The event shall be reported to Stryker and to the IRB/EC, as required.

The following decision tree facilitates identification of AEs for which reporting is required under this study protocol:

Figure 1. Adverse Event Decision Tree

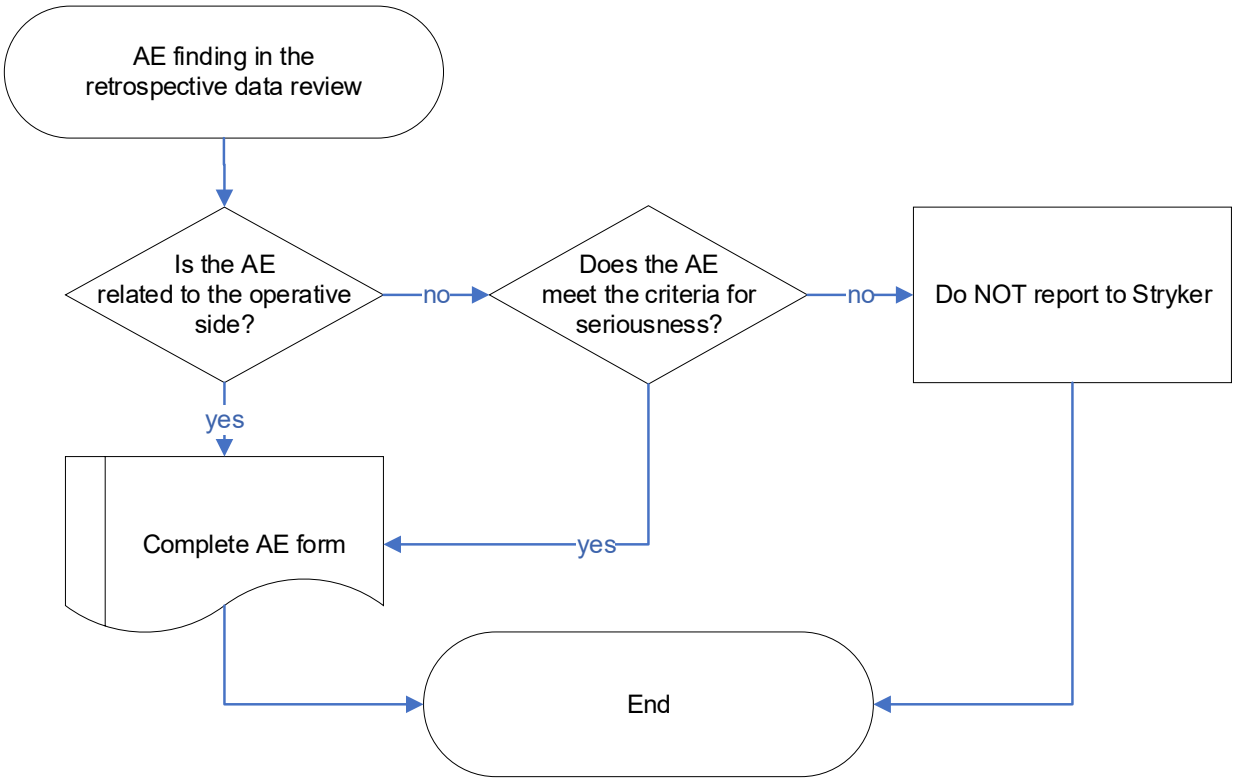


Figure 1 Adverse event decision tree

General Retrospective Review Findings

At screening for inclusion into the study, any clinically significant abnormality should be recorded as a preexisting condition and reported on the Demographics CRF. From the time of surgery forward, any new clinically significant findings or abnormalities that meet the definition of a protocol defined AE must also be recorded and documented as an AE until the end of the observation period or maximum at the five years follow-up.

Adverse Event Reporting Period

The study period during which AEs must be reported is defined as the period from the surgery to the last protocol specified follow-up.

During retrospective review of the subject's hospital files, information on protocol defined AEs shall be recorded in the AE CRF. The clinical course of each event should be followed until resolution or until it is determined at the end of the study that the AE will not resolve.

6.2 General Adverse Event Definitions

Following is a list of general AE definitions. For the purposes of this study, only SAEs, excluding elective procedures, as well as all AEs related to the operative site should be reported.

Adverse Event

An **AE** is any untoward medical occurrence, in a clinical investigation subject which changes the medical baseline of the subject, users or other persons. An AE can be an unfavorable and unintended sign, symptom or disease, whether or not related to the study device (AEs may also be referred to as complications). See Section 6.1, Reporting of Adverse Events, for the AE reporting requirements for this study.

NOTE 1 This definition includes events related to the investigational medical device or the comparator.
NOTE 2 This definition includes events related to the procedures involved.
NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

Anticipated Adverse Event

An **anticipated AE** is an AE, of which the nature, severity or degree of incidence is known and identified in applicable product labeling, published literature or the study protocol. The list of anticipated events is provided in Section 12, Risk/Benefit Assessment.

Serious Adverse Event

A **SAE** meets one or more of the following definitions:

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient or prolonged hospitalization, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- led to foetal distress, foetal death or a congenital abnormality or birth defect

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

Adverse Device Effect

An **adverse device effect** (ADE) is a negative change in the subject's health that may have been caused by, or associated with, the use of the device.

Unanticipated Adverse Device Effect

An **unanticipated adverse device effect** (UADE) is any serious adverse effect on health, safety or any life-threatening problem or death caused by, or associated with, a device if that effect is a problem or death not previously identified in nature, severity or degree of incidence, or any other unanticipated serious problem associated with a device and related to the rights, safety or welfare of subjects.

Device Deficiency

A **device deficiency** is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

a) if either suitable action had not been taken,

b) if intervention had not been made, or

c) if circumstances had been less fortunate

NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.

6.3 Study Sponsor Notification by Investigator

Of reportable AEs, certain events must be submitted to Stryker Orthopaedics within 24 hours for timely notification:

Adverse events that require time sensitive reporting:

An adverse event should be reported to Stryker Orthopaedics Clinical Research either by telephone/fax/email within 24 hours after retrospective finding of the event if any of the following apply:

- The AE occurs intraoperatively or is related to the surgical procedure.
- The AE is considered by the investigator to be Simplex HV related or if the investigator is uncertain regarding the device related assessment;
- The Simplex HV relation requires a reoperation of the Triathlon total knee arthroplasty

At the time of the initial report, the following information should be provided:

• Subject number • A description of the event • Date of onset • Current status	• Whether study treatment was discontinued • Investigator assessment of the association between the event and the study treatment

Table 4 Initial AE report information

These reports will be evaluated by Stryker Orthopaedics to determine if a Product Inquiry (PI) is required.

6.3.1 Ethics Committee/Institutional Review Board Notification by Investigator

Reports of AEs (including follow-up information) must be submitted to the EC or IRB according to their specific requirements. Copies of each report and documentation of EC/IRB notification and receipt will be kept with the investigator's study files.

6.4 Medical Monitoring

It is the responsibility of the investigator to oversee the safety of the study at his/her center. This safety monitoring will include careful assessment and appropriate reporting of AEs, as previously noted. Stryker Orthopaedics will conduct formal investigations via the Product Surveillance Department of those AEs which are submitted through our PI System.

7 X-ray Analysis

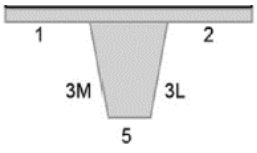
7.1 Definiton of Aseptic Loosening

X-rays will be collected at least at two years after surgery for independent analysis of radiolucency occurence at implant-cement interface by an independent reviewer

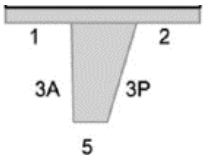
- Radiolucency at implant-cement interface
  - Tibia A/P
  - Tibia lateral
  - Femur PS lateral or Femur CR lateral

Radiolucencies at the implant-cement interface more than 2 mm in all zones of a component is defined as aseptic loosening.

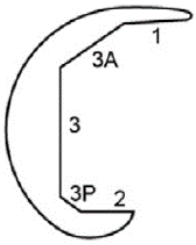
Zones Tibia A/P[7]



Zones Tibia Lateral[7]



Zones Femur PS Lateral[7]



Zones Femur CR Lateral[7]

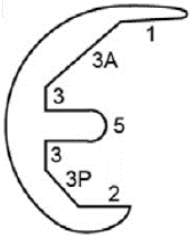


Figure 2 Component zones

8 Data Management

8.1 Database

Paper based data will be collected at each center and entered into Stryker Orthopaedics's data base.

8.2 Confidentiality

This study will comply with the regional privacy rules. As such, Stryker Orthopaedics will only collect that information which is necessary to support the objectives of the clinical study. Stryker

Orthopaedics will take precautions to ensure that data received is de-identified as per regional privacy rules. In the case that some identified information is received, Stryker Orthopaedics will ensure that any identifying information is not publicly disclosed.

8.3 Source Documents

Source data include all information, original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, study worksheets, laboratory notes, memoranda, subject questionnaires, pharmacy dispensing records, recorded data from automated instruments, radiographs, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

Monitors, defined further in Section 10, will be comparing the documentation in CRFs against source documents for adequacy. The monitors will seek to draw a reference between each data point on the CRF and the subject's chart. Every effort should be made to ensure complete source documentation.

8.4 Data Clarification Requests

If errors or omissions are noted by Stryker Orthopaedics upon review of the data entered into the CRFs, a data clarification request (DCR) will be sent to the center. Queries should be answered in a clear and comprehensible manner. If the clarification requires a change to study data, a copy of the DCR will be filed with the CRF.

8.5 Protocol Deviations

Any major deviation from this protocol will be recorded and must be reported to the EC/IRB by the investigational site according to their reporting procedures. Major protocol deviations for this study may include the following; this list may not be all-inclusive:

- Patient enrolled does not meet the inclusion/exclusion criteria
- Protocol specified study component(s) not implanted

8.6 Records Retention

It is the investigator's responsibility to retain study essential documents for two years after the date of the final report, or in the case of non-compliance, two years after the date of investigative center termination. These documents should be retained for a longer period if required by an agreement with Stryker.

9 Statistical Plan

9.1 Study Objectives

9.1.1 Objective Analysis

To evaluate the success rate of cemented Triathlon Total Knee components implanted using Simplex high viscosity bone cement (Simplex HV). Success is defined as absence of revision of cemented Triathlon Total Knee components implanted with Simplex HV for aceptic lossening at two years postoperative. 95% confidence interval of the success rate will be presented as well.

9.2 Safety

9.2.1 Safety Parameters

Safety parameters include all protocol-defined adverse events as well as revision and/or removal rates. For details regarding protocol-defined adverse events, see Section 6.1.

9.2.2 Safety Analyses

The frequency and percentage of all protocol-defined adverse events will be tabulated. For details regarding protocol-defined adverse events, see Section 6.1.

9.3 Missing Data

No missing data will be imputed

9.4 Statistical Methodology

9.4.1 Data Summary

Descriptive statistics will be computed for all baseline conditions and demographic parameters. That is, for continuous data, the N, mean, median, standard deviation, minimum and maximum will be computed. For categorical data, the frequency will be computed. The data will be presented by appropriate subgroups (e.g., center, gender).

A Kaplan-Meier survivorship curve will be displayed for revision and/or removal of the Triathlon total knee arthroplasty cemented with Simplex HV for aseptic loosening.

A Kaplan-Meier survivorship curve will be displayed for all-cause revision and/or removal of the Triathlon total knee arthroplasty cemented with Simplex HV with Gentamicin for aseptic loosening.

Two year Kaplan-Meier success rate with 95% CI will be presented.

For all additional data collected that are not required for direct support of a study objective, data will be summarized according to follow-up. For parameters represented by continuous variables (e.g., ROM), the summaries will consist of the N, mean, median, standard deviation, minimum, and maximum values.

Documentation of statistical analyses utilizing SAS® software version 9.3 or higher will be maintained.

9.4.2 Sample Size Justification

No sample size calculation because a number of 100 cases per study arm was pre-defined by the regulatory body.

9.4.3 Interim Analyses

No interim analysis is planned. Retrospective data up to five years will be analyzed.

9.4.4 Analysis Population

Per Protocol Population: The study population will include all non-censored subjects who have received the Triathlon total knee system cemented with Simplex HV and are available for objective analysis.
The objective analyses will be based on the per protocol population.

Safety Population: The safety population will include all non-censored subjects who received the Triathlon total knee system cemented with Simplex HV.

The safety analysis will be based on the safety population.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

Monitors/Clinical Research Associates (CRAs) are persons employed by sponsors to review the conduct of clinical studies to assure that the clinical investigators abide by their obligations to conduct clinical studies properly. Proper monitoring ensures adequate protection of the rights of human subjects, the safety of subjects involved in a clinical investigation and the quality and integrity of data submitted as a result of the investigation.

This study will be monitored after documentation of retrospective data is done. The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the

Monitor/CRA or other compliance or quality assurance reviewer is given access to all study-related documents and study-related facilities, as applicable, and has adequate space to conduct the monitoring visit, when applicable. The Monitor/CRA will review all source documents and compare them to the data contained in the CRFs, in addition to performing a review of regulatory documents such as EC/IRB approvals. The Monitors/CRAs will need the following:

- An area where they can review study data, when monitoring is conducted on site
- Access to CRF data for all cases
- Access to source documentation
- Regulatory documents
- Time to discuss findings with the SC and the investigator

10.2 Auditing and Inspecting

A quality assurance audit is a form of review that provides additional confidence to the sponsor concerning the validity and accuracy of clinical study data that must be submitted to the regulatory bodies or for publication. The purpose of investigator audits is to ensure that the investigator has maintained all study information according to the sponsor's protocol and standard operating procedures and in compliance with regulations.

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, Stryker Orthopaedics and/or government regulatory bodies of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data). The investigator will ensure the capability for inspections of applicable study-related facilities.

11 Publication Plan

It is anticipated that publication of the multi-center study results of an observation period over two years, with optional five year period, will be compiled and submitted to a peer-reviewed journal. Additional publication proposals may be made by investigators at any time and will be considered.

This study will utilize the guidelines for authorship published by the International Committee of Medical Journal Editors (ICMJE). This guidance can be referenced at www.icmje.org.

Publications will be facilitated by the Chair and the primary investigator (PI) of the study. Both individuals will be chosen by Stryker Orthopaedics.

The PI is solely focused on the multi-center publications and progress towards those publications, including recurring updates to centers, center motivation as well as authorship. If the PI does not

produce a draft of a publication within 90 days of receiving the results data, Stryker Orthopaedics will delegate the responsibility to other investigators in the study at its discretion.

The Chair reviews all additional publications proposed by participating investigators based upon the study results prior to study completion, on an ongoing basis. This review includes whether or not a proposal will be pursued, as well as imposition of guidelines as to publication completion and criteria.

The following summarizes the possible roles of these parallel positions:

Chair	PI
Contributes to study design	Contributes to study design
Assists with study questions requiring expert clinical opinion	Assists with study questions requiring expert clinical opinion
Reviews additional publication proposals submitted by investigators	Updates investigators on progress towards multi-center results
Contributing author, if ICMJE guidelines met	Primary author, multi-center publication of primary endpoint data

Table 5 Possible roles of chair and PI

At the completion of the study, each participating study investigator shall have independent publication privileges for his/her own center's results. Although Stryker will not be involved in coordinating these independent manuscripts, all publications of the data shall be submitted to Stryker for review prior to submission for publication. Stryker shall not edit or otherwise influence the publications other than to ensure that confidential information is not disclosed, that no off-label use of Stryker devices is promoted and that the data is accurately represented. Any publications resulting from this study must be submitted to Stryker for review at least 60 days prior to submission of publication.

12 Risk/Benefit Assessment

12.1 *Risk Category, potential Risk*

There are no additional risks associated as the study is a retrospective review.

12.2 Expected Complications and Rates of Occurrences

In the retrospective data review it can be expected to find known complications.

- Known complications after use of acrylate*:

  Intraoperative:

  Temporary drop in blood pressure immediately after application of cement, pulmonary embolism and mycardial infarctions in rare cases.

Post-operative:

Temporary reduction in blood pressure, elevated blood serum levels diseases of the blood system, loosening of dislocation of the implant, wound infections, cardiovascular and pulmonary diseases, rare cases of anaphylaxis and sudden death.

- Known complications after use of PMMA**:
  Allergic pyrexia, diseases of the urinary system, local neuropathy, vascular diseases, irritation of the siatic nerve.
- Known complications causing from Simplex HV with Gentamicin:
  Hypertensitivity reactions, typical side effects of using Gentamicin which are extremely unlikely to occur because of the very low serum level of Gentamicin.
  For more details see “Adverse event” sections of IFU in **Appendix D**.

* Liquid, see **Tables 2 and 3**

** Powder, see **Tables 2 and 3**

12.3 Potential Benefits to the Subject

There is no guarantee that subjects will personally benefit from the retrospective data review within this study. This study seeks to provide clinicians information about Simplex HV bone cement. Information gathered in this study may benefit others undergoing TKA using Simplex HV bone cement in the future.

13 Ethical Considerations

This study is to be conducted for the protection of human subjects according to international standard ISO 14155 and applicable regional government regulations.

This protocol and any amendments will be submitted to a properly constituted independent EC/IRB for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to Stryker Orthopaedics before commencement of this study. The investigator may be asked to provide a list of EC/IRB members and their affiliates to Stryker Orthopaedics, if available. An EC/IRB confirmation will be applied for waiver of patient information and informed consent due to collection of pseudonymized retrospective patient data.

14 Study Finances

14.1 Funding Source

This study is financed by Stryker.

14.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (e.g. patent ownership, royalties or financial gain greater than the maximum allowable by their institution) must have the conflict reviewed by their EC/IRB or a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by Stryker prior to participation in this study.

14.3 Subject Stipends or Payments

Due to the Retrospective nature of this study, there will be no subject stipend or payment program.

15 References

1. Trends in the Use of High-Viscosity Cement in Patients Undergoing Primary Total Knee Arthroplasty in the United States
   Mick P. Kelly, MD, Richard L. Illgen, MD, Antonia F. Chen, MD, MBA, Denis Nam, MD, MSc
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   Shulin He, Frank Sagato, Robert Klein, Hilda Mulvihill, Yehuda Bogatch
   Stryker CO, Mahwah, NJ, USA, Stryker CO, Limerick, Ireland

3. Low Rates of Aseptic Tibial Loosening in Obese Patients With Use of High-Viscosity Cement and Standard Tibial Tray: 2-Year Minimum Follow-Up
   David A. Crawford, MD, Keith R. Berend, MD, Denis Nam, MD, Robert L. Barrack, MD, Joanne B. Adams, BFA, Adolph V. Lombardi Jr., MD, FACS
   The Journal of Arthroplasty 32 (2017) S183-S186

4. Aseptic Tibial Debonding as a Cause of Early Failure in a Modern Total Knee Arthroplasty Design.
   Arsoy D, Pagnano MW, Lewallen DG, Hanssen AD, Sierra RJ.
   Clin Orthop Relat Res 2013; 471:94e101.

5. Case Series Report: Early Cement–Implant Interface Fixation Failure in Total Knee Replacement
   Kyle J. Hazelwood, Michael O'Rourke, Van P. Stamos, Robert D. McMillan, David Beigler, William J. Robb III
   The Knee 22 (2015) 424–428

6. Failure at the Tibial Cement-Implant Interface with the Use of High Viscosity Cement in Total Knee Arthroplasty.
Kopinski J, Aggarwal A, Nunley R, Barrack R, Nam D
The Journal of Arthroplasty 2016; 31:2579

7. Development of a Modern Knee Society Radiographic Evaluation System and Methodology for Total Knee Arthroplasty
R.Michael Meneghini, Michael A.Mont, David B.Backstein, Doug A.Dennis,
The Journal of Arthroplasty, Volume 30, Issue 12, 2015, 2311-2314

Appendix A Component Listing

Study Device Component Listing:

Catalogue Number
Simplex HV Plain (non-medicated)
6189-1-010
Simplex HV Gentamicin
6193-1-010

Ancillary Component Listing:

Triathlon Cemented Primary Tibial Baseplate
5520-B-100
5520-B-200
5520-B-300
5520-B-400
5520-B-500
5520-B-600
5520-B-700
5520-B-800

Triathlon Symmetric Conventional Polyethylene Patella
5550-L-278
5550-L-298
5550-L-319
5550-L-339
5550-L-360

Triathlon Symmetric X3 Patella
5550-G-278
5550-G-298
5550-G-319
5550-G-339
5550-G-360
5550-G-278-E
5550-G-298-E
5550-G-319-E
5550-G-339-E
5550-G-360-E

Triathlon Asymmetric Conventional Polyethylene Patella
5551-L-299
5551-L-320
5551-L-350
5551-L-381
5551-L-401

Triathlon Asymmetric X3 Patella
5551-G-299
5551-G-320
5551-G-350
5551-G-381
5551-G-401
5551-G-299-E
5551-G-320-E
5551-G-350-E
5551-G-381-E
5551-G-401-E

Triathlon CR Cemented Femur
5510-F-101
5510-F-102
5510-F-201
5510-F-202
5510-F-301
5510-F-302
5510-F-401
5510-F-402
5510-F-501
5510-F-601
5510-F-701
5510-F-801
5510-F-802

Triathlon PS Cemented Femur
5515-F-101
5515-F-102
5515-F-201
5515-F-202
5515-F-301
5515-F-302
5515-F-401
5515-F-402
5515-F-501
5515-F-601
5515-F-701
5515-F-801
5515-F-802

Triathlon CR Conventional Polyethylene Tibial Inserts
5530-P-X09
5530-P-X10
5530-P-X11
5530-P-X12
5530-P-X13
5530-P-X14
5530-P-X16
5530-P-X19

Triathlon CR X3 Tibial Inserts
5530-G-X09
5530-G-X09-E
5530-G-X10-E
5530-G-X11
5530-G-X11-E
5530-G-X12-E
5530-G-X13
5530-G-X13-E
5530-G-X14-E
5530-G-X16
5530-G-X16-E
5530-G-X19
5530-G-X19-E

Triathlon CS Conventional Polyethylene Tibial Inserts
5531-P-X09
5531-P-X10
5531-P-X11
5531-P-X12
5531-P-X13
5531-P-X14
5531-P-X16
5531-P-X19
5531-P-X22

Triathlon CS X3 Tibial Inserts
5531-G-X09
5531-G-X09-E
5531-G-X10-E
5531-G-X11
5531-G-X11-E
5531-G-X12-E
5531-G-X13
5531-G-X13-E
5531-G-X14-E
5531-G-X16
5531-G-X16-E
5531-G-X19
5531-G-X19-E
5531-G-X22-E
5531-G-X25

Triathlon PS Conventional Polyethylene Tibial Inserts
5532-P-X09
5532-P-X10
5532-P-X11
5532-P-X12
5532-P-X13
5532-P-X14
5532-P-X16
5532-P-X19
5532-P-X22

Triathlon PS X3 Tibial Inserts
5532-G-X09
5532-G-X09-E
5532-G-X10-E
5532-G-X11
5532-G-X11-E
5532-G-X12-E
5532-G-X13
5532-G-X13-E
5532-G-X14-E
5532-G-X16
5532-G-X16-E
5532-G-X19
5532-G-X19-E
5532-G-X22-E
5532-G-X25

X= size 1,2,3,4,5,6,7 and 8

Appendix B Case Report Forms

Title page

Simplex HV Bone Cement

A Retrospective Multicenter Study to Review the Use of Simplex High Viscosity Bone Cement in Primary Total Knee Arthroplasty

stryker®

Study # 80

Patient code (Use AA, BB,...AB)		Patient ID	8 0			
			Study #	Center#	Subject #	Side (L/R)

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Simplex HV Retrospective Study

Page 1 of 1 | **INCLUSION / EXCLUSION** | Patient ID 8 0 | Study# | Center# | Subject# | Side (L/R)

GENERAL INFORMATION

Patient code (Use AA, BB,...AB) ☐☐

Date of examination ☐☐/☐☐☐/☐☐☐☐ (D D / M M M / Y Y Y Y)

I. INCLUSION CRITERIA

	Yes	No	
A.	◯	◯	The patient is aged 18 years and over at time of study device implantation.
B.	◯	◯	Patients who have undergone primary Triathlon Total Knee Arthroplasty in which Simplex HV/ Simplex HV Gentamicin was indicated for fixation and used on label.
C.	◯	◯	Patients who have been followed for at least 24 months postoperatively

All of the above must be answered "Yes" for the patient to be enrolled in the study.

II. EXCLUSION CRITERIA

	Yes	No	
A.	◯	◯	Patients who have undergone revision surgery
B.	◯	◯	Patients who have undergone bilateral Knee Arthroplasty
C.	◯	◯	Patients contraindicated for either the devices implanted, or the cement used, according to medical history review and instructions for use.
D.	◯	◯	Patient has a cementless tibial baseplate.
E.	◯	◯	Patient has an active or suspected latent infection in or about the affected knee joint
F.	◯	◯	Patient has muscle loss or neuromuscular impairment in the affected limb that would create an unjustifiable risk.
G.	◯	◯	Patient is immunologically suppressed or receiving steroids in excess of normal physiological requirements (e.g. > 30 days)
H.	◯	◯	Patient has a known hypersensitivity to any of the cements constituents or in patients with severe renal failure
I.	◯	◯	Patient is a prisoner.

All of the above must be answered "No" for the patient to be enrolled in the study.

III. Comments

Investigator Name (Print)

Investigator Signature

Date ☐☐/☐☐☐/☐☐☐☐ (D D / M M M / Y Y Y Y)

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Simplex HV Retrospective Study

Page 1 of 1 | **PRE-OP / DEMOGRAPHICS** | Patient ID: 8 0 (Study#) | (Center#) | (Subject#) | (Side (L/R))

GENERAL INFORMATION

Patient code (Use AA, BB,...AB): ☐☐

Date of examination: D D / M M M / Y Y Y Y

DEMOGRAPHICS

Age ☐☐ | Height ☐☐☐ cm | Weight ☐☐☐ kg | BMI ☐☐.☐ | Gender ◯ male ◯ female

DIAGNOSIS

Patient's Initial Diagnosis: ◯ Osteoarthritis ◯ Post Traumatic Arthritis

Operative side: ◯ left ◯ right

PREOPERATIVE MEDICAL HISTORY (*Relevant concurrent* medical condition and treatment)

	Specify desease	Specify treatment
☐	**Gastrointestinal tract/metabolism**	◯ No treatment ◯ Treatment
☐	**Blood and blood forming organs**	◯ No treatment ◯ Treatment
☐	**Cardiovascular system**	◯ No treatment ◯ Treatment
☐	**Skin**	◯ No treatment ◯ Treatment
☐	**Reproductive system**	◯ No treatment ◯ Treatment
☐	**Endocrine system**	◯ No treatment ◯ Treatment
☐	**Infections and infestations**	◯ No treatment ◯ Treatment
☐	**Malignant/immune disease**	◯ No treatment ◯ Treatment
☐	**Muscles, bones and joints**	◯ No treatment ◯ Treatment
☐	**Brain and nervous system**	◯ No treatment ◯ Treatment
☐	**Respiratory system**	◯ No treatment ◯ Treatment
☐	**Other**	◯ No treatment ◯ Treatment
☐	**Other**	◯ No treatment ◯ Treatment

Investigator Name (Print)

Investigator Signature

Date: D D / M M M / Y Y Y Y

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Simplex HV Retrospective Study

Page 1 of 1 | **Knee Society Score** | Patient ID 8 0 (Study#) ____ (Center#) ____ (Subject#) ____ (Side (L/R))

GENERAL INFORMATION

Patient code (Use AA, BB,...AB) ____

Date of examination ____ / ____ / ____ (D D / M M M / Y Y Y Y)

Pre-op visit ◯ Follow-up at ◯ 12-24 months (+2 months) post study surgery

◯ 5 years (± 3 months) post study surgery, specify ____ years ____ months

1. KSS-PATIENT CATEGORY

◯ Unilateral or bilateral (opposite knee successfully replaced) ◯ Unilateral, Other Knee Symptomatic

◯ Multiple Arthritis or Medical Infirmity (specify)

2. KSS-PAIN/MOTION SCORE

Pain:

◯ None ◯ Moderate occasional

◯ Mild or occasional ◯ Moderate continual

◯ Mild or occasional, stairs only ◯ Severe

◯ Mild or occasional, walking and stairs

ACTIVE Range of Motion:

Neutral Zero Method: ____° / ____° / ____° (Extension / Flexion)

PASSIVE Range of Motion:

Neutral Zero Method: ____° / ____° / ____° (Extension / Flexion)

Stability (amount of motion):

Anteroposterior (Check one) Mediolateral (Check one)

◯ < 5mm ◯ < 5°

◯ 5 - 10 mm ◯ 5° - 9°

◯ > 10mm ◯ 10°-15°

◯ >15°

Alignment (Check one):

◯ Valgus:(please specify degrees) ____

◯ Varus:(please specify degrees) ____

◯ Pain motion score not done

3. KSS-FUNCTION SCORE

Walking aids

◯ None

◯ Cane

◯ Two canes / one crutch

◯ Crutches or walker, cannot walk / wheelchair

Walking

◯ Unlimited

◯ > 10 blocks / >1000m, > 3280 feet

◯ 5-10 blocks / 500m -1000m,1640-3280 feet

◯ < 5 blocks / <500m, <1640 feet

◯ Housebound

Stairs

◯ Normal up & down

◯ Normal up; down with rail

◯ Up & down with rail

◯ Up with rail; unable down

◯ Unable

◯ Function motion score not done

Investigator Name (Print) ____

Investigator Signature ____

Date ____ / ____ / ____ (D D / M M M / Y Y Y Y)

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Stamp Date Received:

INITIAL/DATE

Monitored: ____ / ____

Receipt: ____ / ____

Entry: ____ / ____

Verification: ____ / ____

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Simplex HV Retrospective Study

Page 1 of 2 | **OKS** | Patient ID 8 0 (Study#) | (Center#) | (Subject#) | (Side (L/R))

GENERAL INFORMATION

Patient code (Use AA, BB,...AB) ☐☐

Date of examination ☐☐/☐☐☐/☐☐☐☐ (D D / M M M / Y Y Y Y)

Pre-op visit ◯ Follow-up at ◯ 12-24 months (±2 months) post study surgery

◯ 5 years (± 3 months) post study surgery, specify ☐☐ years ☐☐ months

OKS SCORE

1. How would you describe the pain you usually have in your knee?

◯ None ◯ Very mild ◯ Mild ◯ Moderate ◯ Severe

2. Have you had any trouble washing and drying yourself (all over) because of your knee?

◯ No trouble at all ◯ Very little trouble ◯ Moderate trouble ◯ Extreme difficulty ◯ Impossible to do

3. Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)

◯ No trouble at all ◯ Very little trouble ◯ Moderate trouble ◯ Extreme difficulty ◯ Impossible to do

4. For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)

◯ No pain > 60 min ◯ 16 - 60 minutes ◯ 5 - 15 minutes ◯ Around the house only ◯ Not at all - severe on walking

5. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

◯ Not at all painful ◯ Slightly painful ◯ Moderately pain ◯ Very painful ◯ Unbearable

6. Have you been limping when walking, because of your knee?

◯ Rarely / Never ◯ Sometimes or just at first ◯ Often, not just at first ◯ Most of the time ◯ All of the time

7. Could you kneel down and get up again afterwards?

◯ Yes, easily ◯ With little difficulty ◯ With moderate difficulty ◯ With extreme difficulty ◯ No, impossible

Please continue on page 2 of 2

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Simplex HV Retrospective Study

Page 2 of 2 | **OKS** | Patient ID 8 0 | Study# | Center# | Subject# | Side (L/R)

GENERAL INFORMATION

Patient code (Use AA, BB,...AB)

Date of examination D D / M M M / Y Y Y Y

Pre-op visit ◯ Follow-up at ◯ 12-24 months (±2 months) post study surgery

◯ 5 years (± 3 months) post study surgery, specify ____ years ____ months

OKS SCORE

8. Are you troubled by pain in your knee at night in bed?

Not at all	Only one or two nights	Some nights	Most nights	Every night
◯	◯	◯	◯	◯

9. How much has pain from your knee interfered with your usual work? (including housework)

Not at all	A little bit	Moderately	Greatly	Totally
◯	◯	◯	◯	◯

10. Have you felt that your knee might suddenly give away or let you down?

Rarely / Never	Sometimes or just at first	Often, not at first	Most of the time	All the time
◯	◯	◯	◯	◯

11. Could you do household shopping on your own?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
◯	◯	◯	◯	◯

12. Could you walk down a flight of stairs?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
◯	◯	◯	◯	◯

Investigator Name (Print)

Investigator Signature

Date D D / M M M / Y Y Y Y

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Stamp Date Received:

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Simplex HV Retrospective Study

Page 1 of 2 **INTRA-OPERATIVE** Patient ID 8 0 (Study# | Center# | Subject# | Side (L/R))

GENERAL INFORMATION

Patient code (Use AA, BB,...AB) ☐☐

Surgery date ☐☐/☐☐☐/☐☐☐☐ (D D / M M M / Y Y Y Y)

SURGICAL DETAILS

Type of Anesthesia (check all that apply)

- ◯ Anesthesia: ☐ General ☐ Epidural ☐ Spinal ☐ Femoral Block
- ◯ unknown

Anesthesia Class ASA (check one)

- ◯ ASA class: ◯ 1 excellent ◯ 2 good-moderate ◯ 3 fair ◯ 4 poor
- ◯ unknown

Systemic Prophylactic Therapy

☐ Antibiotic ☐ Anticoagulant ◯ unknown

Surgical Approach (check one)

◯ Medial parapatellar ◯ Sub vastus ◯ unknown
◯ Lateral parapatellar ◯ Mid vastus
◯ Other ☐

Surgeon Initials

☐☐☐ ◯ unknown

Time

Skin to skin ☐☐☐ minutes

Tourniquet ◯ no ◯ yes ◯ unknown

Blood Loss

☐☐☐ ml

◯ unknown

SIMPLEX HV DETAILS

Cement Storing Temperature

Standard cement storing temperature between 0°C/32°F and +25°C/77°F

◯ yes ◯ unknown

Operating Room Temperature

◯ **Hospital standard** select unit ☐☐°C / ☐☐°F

◯ Temperature **less** than 21°C/70°F
◯ Temperature **higher** than 21°C/70°F
◯ Temperature unknown

Cement Type

◯ Simplex HV non-medicated
◯ Simplex HV Gentamycin

Cement Use

Cementless tibial component is exclusion criterion!

☐ Femoral component
☐ Tibial component

Cement Preparation

◯ Hand mixed
◯ Vacuum mixed
◯ unknown

continue on page 2 of 2

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Simplex HV Retrospective Study

Page 2 of 2 **INTRA-OPERATIVE** Patient ID 8 0 Study# Center# Subject# Side (L/R)

GENERAL INFORMATION

Patient code (Use AA, BB,...AB)

Surgery date D D / M M M / Y Y Y Y

TRIATHLON TOTAL KNEE REPLACEMENT DETAILS

Femoral Component

- ◯ **PS** Femoral Component cemented 5515-F-**X**01 left
- ◯ **PS** Femoral Component cemented 5515-F-**X**02 right
- ◯ **CR** Femoral Component cemented 5510-F-**X**01 left
- ◯ **CR** Femoral Component cemented 5510-F-**X**02 right

◯ Size **X:** ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8

Tibial Component

◯ Primary Tibial Baseplate cemented 5520-***B***-**X**00

◯ Size **X:** ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8

◯ Primary MIS Baseplate cemented 5520-M-**X**00

◯ Size **X:** ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8

Tibial Insert

Insert ◯ CR (5530) ◯ CS (5531) ◯ PS (5532)

Material ◯ X3 (G) ◯ Conventional (P)

Height mm ◯ 9 ◯ 11 ◯ 13 ◯ 16 ◯ 19 ◯ 22* ◯ 25* *CS and PS only

Patella

Replaced ◯ No ◯ Yes, specify

Shape ◯ Symmetric (5550) ◯ Asymmetric (5551)

Material ◯ X3 (G) ◯ Conventional (L)

INTRA-OP ADVERSE EVENT / DEVICE DEFICIENCY

◯ No ◯ Yes, complete complication-report

Investigator Name (Print)

Investigator Signature

Date D D / M M M / Y Y Y Y

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Stamp Date Received:

INITIAL/DATE

Monitored: /

Receipt: /

Entry: /

Verification: /

Stryker®

Simplex HV Retrospective Study

Page 1 of 1 **Flollow-up** Patient ID 8 0 (Study#) (Center#) (Subject#) (Side (L/R))

GENERAL INFORMATION

Patient code (Use AA, BB,...AB)

Date of examination D D / M M M / Y Y Y Y

Follow-up at: ◯ 12-24 months (+2 months) post study surgery
◯ 5 years (± 3 months) post study surgery, specify ____ years ____ months

4. X-RAY COLLECTION (A/P and lateral view)

Date of x-ray D D / M M M / Y Y Y Y ◯ x-ray not available

5. ANY OTHER *SCHEDULED* HIP/KNEE JOINT REPLACEMENT SINCE STUDY SURGERY

◯ No ◯ Yes, specify

☐ Contrallat knee, surgery date D D / M M M / Y Y Y Y

☐ Ipsilateral hip, surgery date D D / M M M / Y Y Y Y

☐ Contralateral hip, surgery date D D / M M M / Y Y Y Y

6. *POST-OP* SERIOUS ADVERSE EVENT/DEVICE DEFICIENCY

◯ No ◯ Yes, due to aseptic loosening* ◯ Yes, due to other reason*

*If yes, please specify in **Adverse Event Form**

Investigator Name (Print)

Investigator Signature

Date D D / M M M / Y Y Y Y

For Stryker Use Only

Stamp Date Received:

INITIAL/DATE

Monitored: /

Receipt: /

Entry: /

Verification: /

Stryker®

Simplex HV Retrospective Study

Page 1 of 1 **Knee Society Score** Patient ID 8 0 Study# Center# Subject# Side (L/R)

GENERAL INFORMATION

Patient code (Use AA, BB,...AB) ☐☐

Date of examination ☐☐/☐☐☐/☐☐☐☐ D D M M M Y Y Y Y

Pre-op visit ◯ Follow-up at ◯ 12-24 months (+2 months) post study surgery

◯ 5 years (± 3 months) post study surgery, specify ☐☐ years ☐☐ months

1. KSS-PATIENT CATEGORY

◯ Unilateral or bilateral (opposite knee successfully replaced) ◯ Unilateral, Other Knee Symptomatic

◯ Multiple Arthritis or Medical Infirmity (specify)

2. KSS-PAIN/MOTION SCORE

Pain:

◯ None ◯ Moderate occasional

◯ Mild or occasional ◯ Moderate continual

◯ Mild or occasional, stairs only ◯ Severe

◯ Mild or occasional, walking and stairs

ACTIVE Range of Motion: ☐☐☐°

Neutral Zero Method: ☐☐☐° / ☐☐☐° / ☐☐☐°

Extension Flexion

PASSIVE Range of Motion: ☐☐☐°

Neutral Zero Method: ☐☐☐° / ☐☐☐° / ☐☐☐°

Extension Flexion

Stability (amount of motion):

Anteroposterior (Check one) Mediolateral (Check one)

◯ < 5mm ◯ < 5°

◯ 5 - 10 mm ◯ 5° - 9°

◯ > 10mm ◯ 10°-15°

◯ >15°

Alignment (Check one):

◯ Valgus:(please specify degrees) ☐☐

◯ Varus:(please specify degrees) ☐☐

◯ Pain motion score not done

3. KSS-FUNCTION SCORE

Walking aids

◯ None

◯ Cane

◯ Two canes / one crutch

◯ Crutches or walker, cannot walk / wheelchair

Walking

◯ Unlimited

◯ > 10 blocks / >1000m, > 3280 feet

◯ 5-10 blocks / 500m -1000m,1640-3280 feet

◯ < 5 blocks / <500m, <1640 feet

◯ Housebound

Stairs

◯ Normal up & down

◯ Normal up; down with rail

◯ Up & down with rail

◯ Up with rail; unable down

◯ Unable

◯ Function motion score not done

Investigator Name (Print)

Investigator Signature

Date ☐☐/☐☐☐/☐☐☐☐ D D M M M Y Y Y Y

For Stryker Use Only

Stamp Date Received:

INITIAL/DATE

Monitored: /

Receipt: /

Entry: /

Verification: /

Stryker®

Simplex HV Retrospective Study

Page 1 of 2 | **OKS** | Patient ID 8 0 (Study#) | (Center#) | (Subject#) | (Side (L/R))

GENERAL INFORMATION

Patient code (Use AA, BB,...AB) ☐☐

Date of examination ☐☐/☐☐☐/☐☐☐☐ (D D / M M M / Y Y Y Y)

Pre-op visit ◯ Follow-up at ◯ 12-24 months (±2 months) post study surgery

◯ 5 years (± 3 months) post study surgery, specify ☐☐ years ☐☐ months

OKS SCORE

1. How would you describe the pain you usually have in your knee?

◯ None	◯ Very mild	◯ Mild	◯ Moderate	◯ Severe

2. Have you had any trouble washing and drying yourself (all over) because of your knee?

◯ No trouble at all	◯ Very little trouble	◯ Moderate trouble	◯ Extreme difficulty	◯ Impossible to do

3. Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)

◯ No trouble at all	◯ Very little trouble	◯ Moderate trouble	◯ Extreme difficulty	◯ Impossible to do

4. For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)

◯ No pain > 60 min	◯ 16 - 60 minutes	◯ 5 - 15 minutes	◯ Around the house only	◯ Not at all - severe on walking

5. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

◯ Not at all painful	◯ Slightly painful	◯ Moderately pain	◯ Very painful	◯ Unbearable

6. Have you been limping when walking, because of your knee?

◯ Rarely / Never	◯ Sometimes or just at first	◯ Often, not just at first	◯ Most of the time	◯ All of the time

7. Could you kneel down and get up again afterwards?

◯ Yes, easily	◯ With little difficulty	◯ With moderate difficulty	◯ With extreme difficulty	◯ No, impossible

Please continue on page 2 of 2

Stryker®

Simplex HV Retrospective Study

Page 2 of 2 | **OKS** | Patient ID 8 0 (Study#) | (Center#) | (Subject#) | (Side (L/R))

GENERAL INFORMATION

Patient code (Use AA, BB,...AB) | Date of examination (D D / M M M / Y Y Y Y)

Pre-op visit ◯ | Follow-up at ◯ 12-24 months (±2 months) post study surgery ◯ 5 years (± 3 months) post study surgery, specify ____ years ____ months

OKS SCORE

8. Are you troubled by pain in your knee at night in bed?

◯ Not at all	◯ Only one or two nights	◯ Some nights	◯ Most nights	◯ Every night

9. How much has pain from your knee interfered with your usual work? (including housework)

◯ Not at all	◯ A little bit	◯ Moderately	◯ Greatly	◯ Totally

10. Have you felt that your knee might suddenly give away or let you down?

◯ Rarely / Never	◯ Sometimes or just at first	◯ Often, not at first	◯ Most of the time	◯ All the time

11. Could you do household shopping on your own?

◯ Yes, easily	◯ With little difficulty	◯ With moderate difficulty	◯ With extreme difficulty	◯ No, impossible

12. Could you walk down a flight of stairs?

◯ Yes, easily	◯ With little difficulty	◯ With moderate difficulty	◯ With extreme difficulty	◯ No, impossible

Investigator Name (Print)

Investigator Signature

Date (D D / M M M / Y Y Y Y)

For Stryker Use Only

Stamp Date Received:

INITIAL/DATE:

Monitored: /

Receipt: /

Entry: /

Verification: /

Stryker®

Simplex HV Retrospective Study

Page 1 of 2 | **ADVERSE EVENT REPORT** | Patient ID 8 0 | Study# | Center# | Subject# | Side (L/R)

GENERAL INFORMATION

Patient code (Use AA, BB,...AB)

AE start date D D M M M Y Y Y Y

Occurence: ◯ intra-op ◯ post-op

Adverse Event Information (use one form per complication/event)

Event Description

◯ Aseptic loosening of study device ◯ Other event specify

Date of study surgery D D M M M Y Y Y Y

Date event resolved D D M M M Y Y Y Y ◯ not resolved

Adverse Event Group

◯ Elective Surgery

◯ Operative Site Event

◯ Systemic event

Type of Event please follow protocol chapter 6

◯ AE ◯ SADE

◯ ADE ◯ Device Deficiency

◯ SAE

ISO14155: Planned hospitalization for a preexisting condition, without serious deterioration in health, is not considered a complication/serious adverse event

Seriousness

◯ Not serious

◯ Led to death

◯ Led to serious deterioration in the health of the subject, resulting in:

- ☐ A life-threatening illness or injury
- ☐ A permanent impairment of a body structure or function
- ☐ In-patient or prolonged hospitalization
- ☐ Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- ☐ Led to foetal distress, foetal death or a congenital abnormality or birth defect

Device Relation

◯ yes[1, 2]

◯ no

◯ uncertain[1, 2]

Surgery Relation

◯ yes[1]

◯ no

◯ uncertain[1]

Key

[1]Complete device information on page 2

[2]Verify if complication was reportd to Stryker

Treatment

◯ Revision/Removal due to aseptic loosening of study device

Revision date D D M M M Y Y Y Y

◯ Other operative treatment of operative side, specify

◯ Other treatment, specify

Please continue page 2 of 2

Stryker®

Simplex HV Retrospective Study

Page 2 of 2 | **ADVERSE EVENT REPORT** | Patient ID 8 0 | Study# | Center# | Subject# | Side (L/R)

GENERAL INFORMATION

Patient code (Use AA, BB,...AB)

AE start date D D / M M M / Y Y Y Y

Occurence: ◯ intra-op ◯ post-op

Adverse Event (MedDRA category)

Device Information (if certain or uncertain device or surgery relation)

Component	Ref./Catalogue number	Lot/Case Code
Simplex HV ◯		
Simplex HV, Antibiotic ◯		
Femur component		
Tibilal Component		
Insert		
Patella (if applicable)		

Adverse Event (MedDRA category)

- ◯ Blood and Lymphatic System Disorders
- ◯ Cardiac Disorders
- ◯ Congenital, Familial and Genetic Disorders
- ◯ Ear and Labyrinth Disorders
- ◯ Endocrine Disorders
- ◯ Eye Disorders
- ◯ Gastrointestinal Disorders
- ◯ General Disorders and Administration Site Conditions
- ◯ Hepatobiliary Disorders
- ◯ Immune System Disorders
- ◯ Infections and Infestations
- ◯ Injury, Poisoning and Procedural Complications
- ◯ Investigations
- ◯ Metabolism and Nutrition Disorders
- ◯ Musculoskeletal and Connective Tissue Disorders
- ◯ Neoplasms Benign and Malignant (Incl Cysts and Polyps)
- ◯ Nervous System Disorders
- ◯ Pregnancy, Puerperium and Perinatal Conditions
- ◯ Psychiatric Disorders
- ◯ Renal and Urinary Disorders
- ◯ Reproductive System and Breast Disorders
- ◯ Respiratory, Thoracic and Mediastinal Disorders
- ◯ Skin and subcutaneous Tissue Disorders
- ◯ Social Circumstances
- ◯ Surgical and Medical Procedures
- ◯ Vascular Disorders

Investigator Name (Print)

Investigator Signature

Date D D / M M M / Y Y Y Y

For Stryker Use Only

Stamp Date Received:

INITIAL/DATE:

Monitored: /

Receipt: /

Entry: /

Verification: /

Appendix C 510k Clearance Letters

1. Simplex HV

K123225 1/3

aap Biomaterials GmbH Lagerstraße 11 – 15 64807 Dieburg Germany	**BonOs R** **5. 510(k) Summary**	**164-0034-01** Date of issue: 11.10.2012
	510(k) Premarket Notification PO-34	page 1 of 3

5. 510(k) summary

MAR 15 2013

Preparation date: 11.10.2012

Submitter:
aap Biomaterials GmbH
Lagerstraße 11-15
64807 Dieburg
Germany
Phone: +49 6071 / 929-0
Fax: +49 6071 / 929-100

Contact person: Volker Stirnal

Trade name: BonOs R

Common name: PMMA Bone Cement

Classification: Polymethylmethacrylate (PMMA) Bone Cement
21 CFR 888.3027, Class II

Product Code: LOD

Panel: Orthopedics

Predicate device to which substantial equivalence is claimed:

Manufacturer	Device Name	510(k) #
Heraeus	Palacos R	(K030902)

2/3

aap Biomaterials GmbH Lagerstraße 11 – 15 64807 Dieburg Germany	**BonOs R** **5. 510(k) Summary**	**164-0034-01** Date of issue: 11.10.2012
	510(k) Premarket Notification PO-34	page 2 of 3

Device description:

BonOs R is a fast-setting acrylic resin for use in bone surgery. The bone cement is made of two separate sterile components. When both cement components are mixed together, they become a self hardening, radiopaque bone cement which fixes the implant and transfers stressesevenly to the bone.

Scientific concepts, significant physical and performance characteristics:

Bone cements in general are self-polymerizing two-component systems comprising a powder and a liquid which polymerize at room temperature immediately after they are mixed together.

The major powder component is polymethyl methacrylate / acrylate. Furthermore a radio-opacifier and benzoyl peroxide as an initiator is included.
The liquid mainly consists of methyl methacrylate. It is furthermore comprised of an activator and a stabilizer to prevent premature polymerization.

When the powder and liquid components are mixed together, the activator, DmpT, contained in the liquid activates the initiator in the powder component. This reaction starts the polymerization of the MMA, which is bonded with the polymer powder during ongoing polymerization. A description of polymerization technology is depictured in section 10- Executive summary, annex 10 – A.

As a result, a viscous paste is obtained which can be introduced into bone using a suitable application system. Heat is generated during setting as a result of the progressive polymerization and exothermic reaction respectively. After curing, the bone cement is able to fix the implant. The setting or curing time is greatly influenced by the temperature of the components and environment, which is common for all acrylic bone cements.

Statement of the intended use:

The BonOs R bone cement is intended for use in arthroplastic procedures of the hip, knee and other joints for the fixation of polymer or metallic prosthetic implants to living bone.

Summary of technological characteristics of the new device in comparison to the predicate devices:

BonOs R bone cement comprises the same materials, mechanical safety and performance as the legally marketed device Palacos R.

3/3

aap Biomaterials GmbH Lagerstraße 11 – 15 64807 Dieburg Germany	**BonOs R** **5. 510(k) Summary**	**164-0034-01** Date of issue: 11.10.2012
	510(k) Premarket Notification PO-34	page 3 of 3

Trade Name			**BonOs R**	**Palacos R**
Common name			PMMA Bone Cement	PMMA Bone Cement
Responsible manufacturer			aap Biomaterials	Heraeus Kulzer
510(k) Number			-	K030902
Device Classification Name			Cement, Bone	Cement, Bone
Product Code			LOD	LOD
Classification			Class II	Class II
Regulation no.			21 CFR 888.3027	21 CFR 888.3027
Material	Powder	Polymer	Poly(methyl acrylate, methyl methacrylate)	Poly(methyl acrylate, methyl methacrylate)*
		Initiator	Di-benzoyl peroxide	Di-benzoyl peroxide
		Radiopacifier	Zirconium dioxide	Zirconium dioxide
	Liquid	Monomer	Methylmethacrylate (stabilized with hydroquinone)	Methylmethacrylate (stabilized with hydroquinone)*
		Activator	N,N-dimethyl-p-toluidine	N,N-dimethyl-p-toluidine

* contains Chlorophyll Copper Complex

BonOs R is substantially equivalent to Palacos R (K030902) in regard to intended use, materials and operational principles as a bone cement.
Equivalence was verified by physical, chemical and mechanical comparative tests to Palacos R.

In summary, BonOs R bone cement is as safe and effective for the declared indications as the predicate device, Palacos R.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

March 15, 2013

aap Biomaterials GmbH
% Mr. Volker Stirnal
Director Quality Assurance and Regulatory Affairs
Lagerstrasse 11-15
64807 Dieburg
Germany

Re: K123225
Trade Name: BonOs R
Regulation Number: 21 CFR 888.3027
Regulation Name: Polymethylmethacrylate (PMMA) bone cement
Regulatory Class: Class II
Product Code: LOD
Dated: January 28, 2013
Received: February 1, 2013

Dear Mr. Stirnal:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical

device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Erin D Keith

Mark N. Melkerson
Director
Division of Orthopedic Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

aap Biomaterials GmbH Lagerstraße 11 – 15 64807 Dieburg Germany	**BonOs R** **4. Indications for Use Statement** **510(k) Premarket Notification PO-34**	**164-0033-01** Date of issue:

4. Indications for Use

510(k) Number: K123225

Device Name: BonOs R

Indications for Use:

BonOs R is intended for use in arthroplastic procedures of the hip, knee and other joints for the fixation of polymer or metallic prosthetic implants to living bone.

Prescription Use ____X__ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Laurence D. Coyne -A

(Division Sign-Off)
Division of Orthopedic Devices
510(k) Number: K123225

2. Simplex HV Gentamicin

K123081

1/3

aap Biomaterials GmbH Lagerstraße 11 – 15 64807 Dieburg Germany	**BonOs R Genta**	**164-0059-02**
	5. 510(k) Summary	Date of issue: 07.12.2012
	510(k) Premarket Notification PO-35	page 1 of 3

5. 510(k) summary

MAR 7 2013

Preparation date: 07.12.2012

Submitter:
aap Biomaterials GmbH
Lagerstraße 11-15
64807 Dieburg
Germany
Phone: +49 6071 / 929-0
Fax: +49 6071 / 929-100

Contact person: Volker Stirnal

Trade name: BonOs R Genta

Common name: PMMA Bone Cement

Classification: Polymethylmethacrylate (PMMA) Bone Cement
21 CFR 888.3027, Class II

Product Code: LOD, Bone Cement
MBB, Bone Cement, Antibiotic

Panel: Orthopedics

Predicate device to which substantial equivalence is claimed:

Manufaturer	Device Name	510(k) #
Heraeus	Palacos R+G	(K031673)

2/3

aap Biomaterials GmbH Lagerstraße 11 – 15 64807 Dieburg Germany	**BonOs R Genta** **5. 510(k) Summary**	**164-0059-02** Date of issue: 07.12.2012
	510(k) Premarket Notification PO-35	page 2 of 3

Device description:

BonOs R Genta is a fast-setting acrylic resin with the addition of gentamicin sulfate for use in bone surgery. The bone cement is made of two separate sterile components. When both cement components are mixed together, they become a self hardening, radiopaque bone cement which fixes the implant and transfers stresses evenly to the bone.

Scientific concepts, significant physical and performance characteristics:

Bone cements in general are self-polymerizing two-component systems comprising a powder and a liquid which polymerize at room temperature immediately after they are mixed together.

The major powder component is polymethyl methacrylate / acrylate. Furthermore a radio-opacifier and benzoyl peroxide (as an initiator) is included.
The liquid mainly consists of methyl methacrylate. It is furthermore comprised of an activator and a stabilizer to prevent premature polymerization.

When the powder and liquid components are mixed together, the activator DmpT, contained in the liquid activates the initiator in the powder component. This reaction starts the polymerization of the MMA, which is bonded with the polymer powder during ongoing polymerization. A description of polymerization technology is depictured in section 10- Executive summary, annex 10 – D.

As a result, a viscous paste is obtained which can be introduced into bone using a suitable application system. Heat is generated during setting as a result of the progressive polymerization and exothermic reaction respectively. After curing, the bone cement is able to fix the implant. The setting or curing time is greatly influenced by the temperature of the components and environment, which is common for all acrylic bone cements.

Statement of the intended use:

The BonOs R Genta bone cement is intended for use in arthroplastic procedures of the hip, knee and other joints for the fixation of polymer or metallic prosthetic implants to living bone when reconstruction is necessary because of revision of previous arthroplasty procedures due to joint infection. The cement is intended for use to affix a new prosthesis in the second stage of a two-stage revision after the initial infection has been cleared.

3/3

Summary of technological characteristics of the new device in comparison to the predicate devices:

BonOs R Genta bone cement comprises the same materials, mechanical safety and performance as the legally marketed devices Palacos R+G.

Trade Name			**BonOs R Genta**	**Palacos R+G**
Common name			PMMA Bone Cement	PMMA Bone Cement
Responsible manufacturer			aap Biomaterials	Heraeus Kulzer
510(k) Number			-	K031673
Device Classification Name			Cement, Bone	Cement, Bone
Product Code			LOD, MBB	LOD, MBB
Classification			Class II	Class II
Regulation no.			21 CFR 888.3027	21 CFR 888.3027
Material	Powder	Polymer	Poly(methyl acrylate, methyl methacrylate)	Poly(methyl acrylate, methyl methacrylate)*
		Initiator	Di-benzoyl peroxide	Di-benzoyl peroxide
		Radiopacifier	Zirconium dioxide	Zirconium dioxide
		Antibiotic	Gentamicin	Gentamicin
	Liquid	Monomer	Methylmethacrylate (stabilized with hydroquinone)	Methylmethacrylate (stabilized with hydroquinone)*
		Activator	N,N-dimethyl-p-toluidine	N,N-dimethyl-p-toluidine

* contains Chlorophyll Copper Complex

BonOs R Genta is substantially equivalent to Palacos R Genta (K031673) in regard to intended use, materials and operational principles as a bone cement. Equivalence was verified by physical, chemical and mechanical comparative tests to Palacos R+G.

In summary, BonOs R Genta bone cement is as safe and effective for the declared indications as the predicate devices Palacos R+G.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

March 7, 2013

aap Biomaterials GmbH
% Mr. Volker Stirnal
Director Quality Assurance and Regulatory Affairs
Lagerstrasse 11-15
64807 Dieburg
Germany

Re: K123081
Trade Name: BonOs R Genta
Regulation Number: 21 CFR 888.3027
Regulation Name: Polymethylmethacrylate (PMMA) Bone Cement
Regulatory Class: Class II
Product Code: LOD, MBB
Dated: January 25, 2013
Received: January 28, 2013

Dear Mr. Stirnal:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set

forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Erin D Keith

Mark N. Melkerson
Director
Division of Orthopedic Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

aap Biomaterials GmbH Lagerstraße 11 – 15 64807 Dieburg Germany	**BonOs R Genta** **4. Indications for Use Statement** **510(k) Premarket Notification PO-35**	**164-0058-01** Date of issue: 27.09.2012

4. Indications for Use

510(k) Number: K123081

Device Name: BonOs R Genta

Indications for Use:

BonOs R Genta is intended for use in arthroplastic procedures of the hip, knee and other joints for the fixation of polymer or metallic prosthetic implants to living bone when reconstruction is necessary because of revision of previous arthroplasty procedures due to joint infection. The cement is intended for use to affix a new prosthesis in the second stage of a two-stage revision after the initial infection has been cleared.

Prescription Use ____X__ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Laurence D. Coyne -A

(Division Sign-Off)
Division of Orthopedic Devices
510(k) Number: K123081

Appendix D Instructions for Use

1. Simplex HV

Radiopaque synthetic resin for use in bone surgery

Purpose and properties
Simplex® HV is a fast-setting acrylic resin for use in bone surgery. Mixing the two separate sterile components produces a ductile bone cement which, after hardening, fixes the implant and transfers stresses produced during movement evenly to the bone. Simplex® HV cement powder also contains insoluble zirconium dioxide as an X-ray contrast medium. Simplex® HV does not emit a signal and does not pose a safety risk in a magnetic resonance environment.

Composition Simplex® HV
The cement powder contains

	40 g
Poly (methylacrylate/methylmethacrylate)	33.7 g
Zirconium dioxide	6 g
Benzoyl peroxide	0.3 g

The liquid component contains

	20 ml
Methylmethacrylate (stabilized with 60 ppm HQ)	18.4 g
N,N-dimethyl-p-toluidine	0.4 g

Indications
In partial or total replacement of the hip, knee and other joints, Simplex® HV is indicated for fixation of synthetic resin polymer and metal prosthesis components in uninfected vital bones if joint reconstruction is required.
In tumour surgery, Simplex® HV is used in combination with internal fixation to fill bone cavities after tumour removal.

Contraindications
The use of Simplex® HV is contraindicated if muscle wasting or neuromuscular compromise in the affected limb renders the procedure unjustifiable. Simplex® HV should not be used in the event of known hypersensitivity to any of its constituents or if active or inadequately treated infections in the region of the implant.

Information for use
Before using Simplex® HV for the first time, surgeons should familiarise themselves with the mixing and application process. A trial run of the mixing process is recommended. If special mixing and application techniques are to be used, the surgeon must read the relevant instructions first.
The protective outer packaging (aluminium/PE pouch) and blister pack containing the ampoule should be removed from the carton in the non-sterile area. After removal from the protective outer packaging, the polyethylene pouch ("peel-off pouch"), the outside of which is not sterile, and the blister pack containing the ampoule are opened one after the other in sterile conditions by a circulating nurse and passed to a member of the surgical team in the sterile area. After careful preparation of the implant site, the cement can be applied to the bone manually, using a cement syringe or with other application systems (details of how to do this can be found in the instructions for the system used). The ampoule is opened by breaking its neck and the inner pouch containing the cement powder cut open using sterile scissors.

Dosage
The amount of Simplex® HV required depends on the anatomical conditions of the patient and the implant used. If a large amount is needed, additional packs (powder and monomer) may be mixed together. However, at least one complete unit (the contents of one pouch and one ampoule) must always be mixed. In total, no more than 160 g should be mixed at once. It is advisable to keep additional packs of Simplex® HV ready as a precaution.

Tools required for mixing Simplex® HV
Sterile working area, sterile porcelain bowls, stainless steel bowls or plastic bowls that are suitable for monomers, sterile mixing spoons or spatulas made of porcelain or high-grade steel, or a sterile mixing system for bone cements. To utilize a modern cementing technique, use a vacuum mixing system.

Manual mixing and application
To make the mixture, empty the entire contents of the required ampoules into a suitable sterile, inert mixing vessel. Then add the entire contents of the corresponding number of packs of powder to the liquid and, using a suitable spatula, carefully mix the components for about 30 seconds until the powder has completely absorbed the liquid and a homogenous mixture has formed. The cement can be applied when it stops sticking to the surgeon's gloves and has reached the desired viscosity. The application phase ends when the mixture becomes rubbery and elastic and no longer binds completely when kneaded.
If application of the cement continues, even filling of the bone cannot be ensured and there is a risk that the implant will loosen prematurely (see Fig. 1).

Vacuum mixing
In order to reduce porosity, the cement can be mixed in a vacuum mixing system. The prechilling is not mandatorily necessary. Simplex® HV is designed for handling between 17°C and 25°C, however, prechilling is recommended. The mixing time should be approximately 30 seconds. The contents of the required ampoules are placed in the mixing vessel and the corresponding number of powder units added. The further procedure can be found in the instructions supplied by the manufacturer of the mixing system (see Fig. 2).

Prechilling
Prechilling is recommended if a lower viscosity or a prolonged handling time of the bone cement is required. Prechilling of the bone cement for at least 24 hours reduces the viscosity of the bone cement. To obtain optimal results store the cement components at 4°C for at least 24 hours. The mixing time is also 30 seconds, however the application and hardening phase is longer. Prechilling is recommended for vacuum mixing (see Fig. 3).

Application with a cement syringe
For several minutes after mixing, the cement can be applied with a syringe, although the process must be monitored carefully by the surgeon due to the increasing viscosity over time. In hip joint replacement, the use of a restrictor or plug in the femoral canal is strongly recommended.

Notes on use
1. For good fixation of the implant, it should be inserted during the application phase and held in place until the cement hardens.
2. Surplus cement should be removed before it hardens.
3. The temperature-time graphs should be noted.
4. Pre-chilling the cement components reduces viscosity and prolongs handling and hardening time.
5. Prechilling of the cement components at 4°C is recommended when mixed with a vacuum mixing device.
6. Handling time and polymerisation are heavily dependent on the temperature of the components and environment. Hardening time is reduced by higher temperatures and prolonged by lower temperatures. Viscosity increases with the progression of polymerisation, i.e. the duration of the handling phase.
7. The addition of any other powders or liquids can reduce solidity and impair handling characteristics and must therefore be avoided.
8. During mixing and application it is important to minimize air entrapment.
9. The powder and liquid components have been carefully designed to complement each other. The entire contents of the pouch and ampoule must always be mixed.
   USING ONLY PARTS OF THE COMPONENTS IS NOT PERMITTED!

10. It is recommended to verify the correct implantation with suitable imaging procedures.
11. If the cement is applied premature to the recommended instruction for use bleeding pressure may cause blood to intrude into the cement mass and may change the mechanical properties of the bone cement.

Use in joint surgery
When using Simplex® HV in joint surgery, a modern cementing technique should be used in order to limit undesirable effects. A prerequisite for this is careful preparation of the implant site with thorough rinsing (e.g. pulsatile lavage) and drying before application of the cement. In order to prevent pressure from building in the medullary canal during implantation, adequate drainage is recommended. Further prerequisites for better fixation of the implant include filling the entire medullary canal with cement using a restrictor, completely surrounding the implant with a cement mantle (ideally 2-5 mm thick) and achieving the ideal biomechanical fit in the bone.

Use in tumour surgery
After removal of the tumour, bone cavities are filled with Simplex® HV. Plates or screws are then inserted to ensure the necessary stability.

Adverse events
After preparation of the implant site and immediately after application of cement and implantation, the rise in pressure in the medullary canal can lead to a temporary drop in blood pressure. In rare cases, pulmonary embolism and myocardial infarction are also observed. These cardiovascular and respiratory side effects, which are known as **implantation syndrome**, result mainly from infiltration of bone marrow constituents into the venous system.
The following additional undesirable effects have occurred after using acrylate cements: temporary reduction in blood pressure, elevated serum levels of gamma-glutamyl transferase (gamma-GT) up to 10 days after surgery, thrombophlebitis, hemorrhage and haematoma, loosening or dislocation of the implant, superficial or deep wound infection, trochanteric bursitis, heterotopic ossification and trochanteric detachment, cardiovascular reactions such as temporary heart rhythm disorders, short-term cardiac conduction irregularities, arrhythmia, myocardial infarction and cardiac arrest, hypoxaemia, bronchospasm, pulmonary embolism, apoplexy.
There have been rare reports of hypotension with anaphylaxis including anaphylactic shock associated with cardiac arrest and sudden death.
Other adverse events that may be linked to the use of PMMA bone cements are: allergic pyrexia, haematuria, dysuria, bladder fistulas, local neuropathy and vascular erosion or occlusion as well as postoperative irritation of the sciatic nerve because bone cement has been placed outside the intended area of application.
Monomer vapours can irritate the respiratory tract and eyes and may damage organs.

Warnings and precautions

Use during pregnancy and lactation
There are no adequate studies of the use of acrylate cements during pregnancy and lactation or of their effect on human fertility. During pregnancy and lactation the surgeon should weigh the benefit for the mother against the potential risk to the child before using Simplex® HV bone cement.

Warnings relating to the age of the patients to be treated
There are no adequate studies on the use of acrylate cements in children. As the possibility of acrylate cements having adverse effects on bone growth cannot be ruled out, the use of Simplex® HV in children and patients who are still growing is inadvisable.
As reported in the clinical literature, in younger patients, cementless components perform as well or better then cemented components.
During and immediately after application of the bone cement/implantation, blood pressure, pulse and respiration must be monitored carefully and appropriate measures taken if significant changes occur. If the patient develops pulmonary or cardiovascular symptoms, appropriate monitoring of blood loss is required. In the event of acute respiratory failure, anaesthesiological measures should be initiated immediately.
Hypotensive reactions have occurred between 10 and 165 seconds following application to bone;

they have lasted from 30 seconds to 5 or more minutes. Some have progressed to cardiac arrest.
Polymerisation (hardening) of Simplex® HV is an exothermic reaction. The heat given off during this reaction may damage bone or other tissue in the region of the implant.
The training and experience of the surgeon are very important when handling acrylate bone cements. Instructions for handling and mixing the cement and preparing the implant site must be followed carefully. Before using Simplex® HV, the surgeon must be thoroughly familiar with its properties and handling characteristics. As the handling and setting characteristics of Simplex® HV depend on the temperature and mixing technique, they are best determined by the surgeon on the basis of actual experience. For this reason, the surgeon is strongly recommended to carry out a trial run of the entire mixing, handling and setting process before performing a surgical procedure with Simplex® HV.
Inadequate fixation and unexpected postoperative events impair the interface between the cement and bone. This can cause micro-movements, which may lead to the formation of a layer of fibrous tissue and premature implant failure. Premature loosening of the implant in the cement mantle is also possible. Therefore, long-term regular follow-up examinations are recommended for all patients.
Methyl methacrylate is a slightly volatile, flammable liquid. The vapours produced during the mixing process can irritate the respiratory tract and eyes and cause general malaise and headache. Such symptoms can be reduced with adequate ventilation or by using closed mixing systems. The monomer (methyl methacrylate) is lipid-soluble. Direct skin contact with the liquid monomer should be avoided as far as possible, as allergic reactions (contact dermatitis) cannot be ruled out. It is therefore advisable to wear an additional pair of polyethylene (PE) gloves under normal surgical gloves when handling the cement. The following materials have also proved to be suitable for protective gloves: PVP (polyethylene, ethylene vinyl alcohol, polyethylene) and viton butyl.
Contact lenses should be protected from the escaping monomer vapours.

Storage
Simplex® HV should be stored away from direct sunlight. Simplex® HV is stored at temperatures between 0°C (32°F) and +25°C (77°F). Do not use Simplex® HV after the expiry date.

Shelf life/sterility
The expiry date is printed on the outer carton and on the patient label. Simplex® HV must not be used after this date. The contents of unused open or damaged packs must not be resterilised and should therefore be discarded. The polymer powder must not be used if it shows yellow discolouration. The liquid monomer, the ampoule itself, the inside of the blister, the cement powder and the inner PE/paper pouch are all sterile. The product must not be used if the packaging is damaged.

SINGLE-USE
Simplex® HV must never be reused. Due to the functionality (hardening) of PMMA bone cements Simplex® HV is only suitable for use within the specified application period. One unit of Simplex® HV must be used for only one single patient.

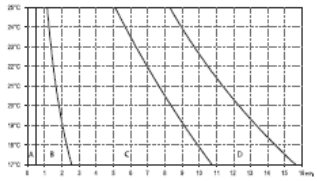
Safe disposal
1. Mixed cement should set before it is discarded with hospital waste.
2. For separate disposal of powder and liquid, please ask local waste disposal authorities.

Information
For further information, please contact your supplier or the manufacturer directly.

Symbol definitions

Manufacturer	Consult instructions for use
Use-by date	Caution
Batch code	CE marking of conformity
Catalogue number	Registered trademark
Sterilized using aseptic processing techniques	Flammable
Sterilized using ethylene oxide	Harmful
Do not resterilize	Health Hazard
Do not use if package is damaged	Ampoule
Keep away from sunlight	Blister
Temperature limit	Pouch
Do not re-use	

Fig. 1: Manual Mixing



A: Mixing phase
B: Waiting phase
C: Application phase
D: Hardening phase

Fig. 2: Vacuum Mixing

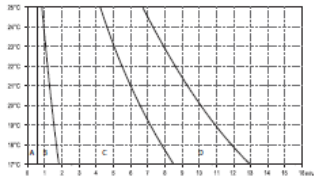
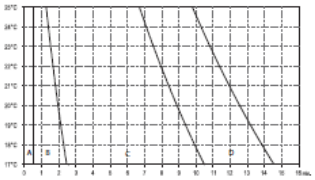


Fig. 3: Prechilled Vacuum Mixing



[1] Different mixers may have different effects on the properties of the bone cement

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2. Simplex HV Gentamicin

Radiopaque synthetic resin for use in bone surgery

Purpose and properties
Simplex® HV with Gentamicin is a fast-setting acrylic resin with addition of gentamicin sulfate for use in bone surgery. Mixing the two separate sterile components produces a ductile bone cement which, after hardening, fixes the implant and transfers stresses produced during movement evenly to the bone. The added antibiotic, gentamicin sulfate, protects the implant and the surrounding tissue from colonization with pathogens that are sensitive to gentamicin. Simplex® HV with Gentamicin cement powder also contains insoluble zirconium dioxide as an X-ray contrast medium. Simplex® HV with Gentamicin does not emit a signal and does not pose a safety risk in a magnetic resonance environment.

Composition Simplex® HV with Gentamicin

The cement powder contains	40.8 g
Poly (methylacrylate/ methylmethacrylate)	33.7 g
Zirconium dioxide	6 g
Benzoyl peroxide	0.3 g
Gentamicin base (added as Gentamicin sulfate)	0.5 g (0.8 g)

The liquid component contains	20 ml
Methylmethacrylate (stabilized with 60 ppm HQ)	18.4 g
N,N-dimethyl-p-toluidine	0.4 g

The instructions for Use provided in this package are not applicable to Canada. Please refer to www.stryker.ca for the Canadian Instructions for Use.

Indications
Simplex® HV with Gentamicin is indicated for fixation of synthetic resin and metal prosthesis components during partial or total replacement of the hip and knee as well as other joints, if an infection with organisms that are sensitive to gentamicin is diagnosed or suspected. The antibiotic provides protection against bacterial colonization of the implant and the surrounding tissue.
Simplex® HV with Gentamicin can be used for filling and stabilizing bone defects within the scope of internal fixation treatment, if there is an increased risk of infection with pathogens that are sensitive to gentamicin.

Contraindications
The use of Simplex® HV with Gentamicin is contraindicated, if muscle wasting or neuromuscular compromise in the affected limb renders the procedure unjustifiable. Simplex® HV with Gentamicin should not be used in the event of known hypersensitivity to any of its constituents or in patients with severe renal failure.

Information for use
Before using Simplex® HV with Gentamicin for the first time, surgeons should familiarize themselves with the mixing and application process. A trial run of the mixing process is recommended. If special mixing and application techniques are to be used, the surgeon must read the relevant instructions first. The protective outer packaging (aluminum/PE pouch) and blister pack containing the ampoule should be removed from the carton in the non-sterile area. After removal from the protective outer packaging, the polyethylene pouch ("peel-off pouch"), the outside of which is not sterile, and the blister pack containing the ampoule are opened one after the other under strict aseptic technique by a circulating nurse and passed to a member of the surgical team in the sterile area. After careful preparation of the implant site, the cement can be applied to the bone manually, using a cement syringe or with other application techniques (details of how to do this can be found in the instructions for the system used). The ampoule is opened by breaking its neck and the inner pouch containing the cement powder cut open using sterile scissors.

Dosage
The amount of Simplex® HV with Gentamicin required depends on the anatomical conditions of the patient and the implant used. If a large amount is needed, additional packs (powder and monomer) may be mixed together. However, at least one complete unit (the contents of one pouch and one ampoule) must always be mixed. In total, no more than 160 g should be applied at once. It is advisable to keep additional packs of Simplex® HV with Gentamicin ready as a precaution.

Tools required for mixing Simplex® HV with Gentamicin
Sterile working area, sterile porcelain bowls, stainless steel bowls or plastic bowls that are suitable for

monomers, sterile mixing spoons or spatulas made of porcelain or high-grade steel, or a sterile mixing system for bone cements. To utilize a modern cementing technique, the use a vacuum mixing system is recommended.

Manual mixing and application
To make the mixture, empty the entire contents of the required ampoules into a suitable sterile, inert mixing vessel. Then add the entire contents of the corresponding number of packs of powder to the liquid and, using a suitable spatula, carefully mix the components for about 30 seconds until the powder has completely absorbed the liquid and a homogenous dough has formed. The cement can be applied when it stops sticking to the surgeon's gloves and has reached the desired viscosity. The application phase ends when the dough becomes rubbery and elastic and no longer binds completely when kneaded. If, application of the cement continues, even filling of the bone cannot be ensured and there is a risk that the implant will loosen prematurely (see Fig. 1).

Vacuum mixing
In order to reduce porosity, the cement can be mixed in a vacuum mixing system. Simplex® HV with Gentamicin is designed for handling between 17°C and 25°C, however, prechilling is recommended. The mixing time should be approximately 30 seconds. The contents of the required ampoules are emptied into the mixing vessel and the corresponding number of powder units added. The further procedure can be found in the instructions, supplied by the manufacturer of the mixing system (see Fig. 2).

Prechilling
Prechilling is recommended if a lower viscosity or a prolonged handling time of the bone cement is required. Prechilling of the bone cement for at least 24 hours makes mixing more convenient and reduces the viscosity of the bone cement. The mixing time is also 30 seconds, however the application and hardening phase is longer. With decrease in temperature, viscosity decreases and handling as well as hardening time increase. For handling characteristics at for example 4°C please refer to fig. 3. Do not prechill Simplex® HV with Gentamicin at temperatures below 4°C.

Application with a cement syringe
For several minutes after mixing, the cement can be applied with a syringe, although the process must be monitored carefully by the surgeon due to the increasing viscosity over time. In hip joint replacement, the use of a restrictor or plug in the femoral canal is strongly recommended.

Notes on use
1. For a good fixation the implant should be inserted during the application phase and held in place until the cement hardens.
2. Surplus cement should be removed before it hardens.
3. The temperature-time graphs should be noted.
4. Prechilling the cement components reduces viscosity and prolongs handling and hardening time.
5. Prechilling of the cement components at 4°C is recommended when mixed with a vacuum mixing device.
6. Handling time and polymerization are heavily dependent on the temperature of the components and environment. Hardening time is reduced by higher temperatures and prolonged by lower temperatures. Viscosity increases with the progression of polymerization, i.e. the duration of the handling phase.
7. The addition of any other powders or liquids can reduce solidity and/or impair handling characteristics and must therefore be avoided.
8. During mixing and application it is important to minimize air entrapment.
9. The powder and liquid components have been carefully designed to complement each other. The entire contents of the pouch and ampoule must always be mixed.
   USING ONLY PARTS OF THE COMPONENTS IS NOT PERMITTED!
10. It is recommended to verify the correct implantation with suitable imaging procedures.
11. If the cement is applied in a too low viscous state the bleeding pressure can intrude into the cement mass and can lower the longevity of the implant.

Use in joint surgery
When using Simplex® HV with Gentamicin in joint surgery, a modern cementing technique should be

used to limit undesirable effects. A prerequisite for this is careful preparation of the implant site with thorough rinsing (e.g. pulsatile lavage) and drying before application of the cement. In order to prevent pressure from building in the medullary canal during implantation, adequate drainage is recommended. Further prerequisites for better fixation of the implant include filling the entire medullary canal with cement using a restrictor, completely surrounding the implant with a cement mantle (ideally 2-5 mm thick) and achieving the ideal biomechanical fit in the bone.

Filling of bone defects
Bone defects are filled with Simplex® HV with Gentamicin. Plates or screws are then inserted to ensure the necessary stability.

Adverse events
After preparation of the implant site and immediately after application of cement and implantation, the rise in pressure in the medullary canal can lead to a temporary drop in blood pressure. In rare cases, pulmonary embolism and myocardial infarction are also observed. These cardiovascular and respiratory side effects, which are known as implantation syndrome, result mainly from infiltration of bone marrow constituents into the venous system.
The following additional undesirable effects have occurred after using acrylate cements: temporary reduction in blood pressure, elevated serum levels of gamma-glutamyl transferase (gamma-GT) up to 10 days after surgery, thrombophlebitis, hemorrhage and hematoma, loosening or dislocation of the implant, superficial or deep wound infection, trochanteric bursitis, heterotopic ossification and trochanteric detachment, cardiovascular reactions such as temporary heart rhythm disorders, short-term cardiac conduction irregularities, arrhythmia, myocardial infarction and cardiac arrest, hypoxemia, bronchospasm, pulmonary embolism, apoplexy.
There have been rare reports of hypotension with anaphylaxis including anaphylactic shock associated with cardiac arrest and sudden death.
Other adverse events that may be attributable to the use of PMMA bone cements are: allergic pyrexia, hematuria, dysuria, bladder fistulas, local neuropathy and vascular erosion or occlusion as well as postoperative irritation of the sciatic nerve, because bone cement has been placed outside the intended area of application.
In isolated cases, the gentamicin contained in Simplex® HV with Gentamicin can cause hypersensitivity reactions. In principle, the typical side effects of using gentamicin, particularly hearing problems and kidney damage, cannot be ruled out completely.
However, these side effects are extremely unlikely to occur, because of the very low serum level of gentamicin (<1 µg/ml).
Monomer vapors can irritate the respiratory tract and eyes and may damage organs.

Interactions
The tendency of gentamicin to block neuromuscular transmission can be intensified by concomitant administration of muscle relaxants, e.g. D-tubocurarine, suxamethonium or pancuronium, as well as by ether. Concomitant administration of potentially neurotoxic and/or nephrotoxic substances, e.g. cisplatin, other aminoglycosides, streptomycin, cefaloridine, viomycin, polymyxin B or polymyxin E, can increase the toxicity of gentamicin. However, interaction is very unlikely to occur because of the low serum levels of gentamicin.

Warnings and precautions

Use during pregnancy and lactation
There are no adequate studies of the use of acrylate cements during pregnancy and lactation or of their effect on human fertility. During pregnancy and lactation the surgeon should weigh the benefit for the mother against the potential risk to the child before using Simplex® HV with Gentamicin bone cement.

Warnings relating to the age of the patients to be treated
There are no adequate studies on the use of acrylic bone cements in children. As the possibility of acrylate cements having adverse effects on bone growth cannot be ruled out, the use of Simplex® HV with Gentamicin in children and patients who are still growing is inadvisable.
As reported in the clinical literature, in younger patients, cementless components perform as well or better then cemented components.
During and immediately after application of the bone cement/implantation, blood pressure, pulse and respiration must be monitored carefully and appropriate measures taken, if significant changes occur. If the patient develops pulmonary or cardiovascular symptoms, appropriate monitoring of blood loss is required. In the event of acute respiratory failure, anesthesiological measures should be initiated immediately.

Hypotensive reactions have occurred between 10 and 165 seconds following application to bone; they have lasted from 30 seconds to 5 or more minutes. Some have progressed to cardiac arrest.
Polymerization (hardening) of Simplex® HV with Gentamicin is an exothermic reaction. The heat given off during this reaction may damage bone or other tissue in the region of the implant.
The training and experience of the surgeon are very important when handling acrylate bone cements. Instructions for handling and mixing the cement and preparing the implantion site must be followed carefully. Before using Simplex® HV with Gentamicin, the surgeon must be thoroughly familiar with its properties and handling characteristics. As the handling and setting characteristics of Simplex® HV with Gentamicin depend on the temperature and mixing technique, they are best determined by the surgeon on the basis of actual experience. For this reason, the surgeon is strongly recommended to carry out a trial run of the entire mixing, handling and setting process before performing a surgical procedure with Simplex® HV with Gentamicin.
Inadequate fixation and unexpected postoperative events impair the interface between the cement and bone. This can cause micro-movements, which may lead to the formation of a layer of fibrous tissue and premature implant failure. Premature loosening of the implant in the cement mantle is also possible. Therefore, long-term regular follow-up examinations are recommended for all patients.
Whenever clinically indicated additional appropriate systemic antibiotic coverage should be used on the day of surgery. Careful consideration should be given to the potential additional safety aspects of the additional antibiotics.
Methyl methacrylate is a volatile, flammable liquid. The vapors produced during the mixing process can irritate the respiratory tract and eyes and cause general malaise and headache. Such symptoms can be reduced with adequate ventilation or by using closed mixing systems. The monomer (methyl methacrylate) is lipid-soluble. Direct skin contact with the liquid monomer should be avoided as far as possible, as allergic reactions (contact dermatitis) cannot be ruled out. It is therefore advisable to wear an additional pair of polyethylene (PE) gloves under the normal surgical gloves when handling the cement. The following materials have also proved to be suitable for protective gloves: PVP (polyethylene, ethylene vinyl alcohol, polyethylene) and viton butyl.
Contact lenses should be protected from the escaping monomer vapors.
The time point when the prosthesis or the filled bone defect can be fully loaded, as well as precautions and actions to be avoided after surgery depends on the surgical procedure, the type of associated implant and the condition of the patient and should be judged by the responsible surgeon. Medical staff must inform the patient of all precautions to be taken.

Removal of bone cement in case of revision
For revision, a radical debridement that entitles removal of cement, and potentially infected and devitalized tissue is performed. Intramedullary reaming of the canal followed with copious use of saline pulse lavage is recommended. The procedure to remove the implant is a case by case decision by the responsible surgeon depending on the condition of the implant and the patient.

Storage
Simplex® HV with Gentamicin should be stored away from direct sunlight. Simplex® HV with Gentamicin is stored at temperatures between 0°C (32°F) and +25°C (77°F). Do not use Simplex® HV with Gentamicin after the expiry date.

Shelf life/sterility
The expiry date is printed on the outer carton and on the patient label. Simplex® HV with Gentamicin must not be used after this date. The contents of unused open or damaged packs must not be resterilized and should therefore be discarded. The polymer powder must not be used, if it shows yellow discoloration. The liquid monomer (aseptically filled), the ampoule itself (outside sterilized using ethylene oxide), the inside of the blister (sterilized using ethylene oxide), the cement powder and the inner PE/paper pouch are all sterile.

Single-use
Simplex® HV with Gentamicin must never be reused. Due to the functionality (hardening) of PMMA bone cements, Simplex® HV with Gentamicin is only suitable for use within the specified application period. One unit of Simplex® HV with Gentamicin must be used for only one single patient.

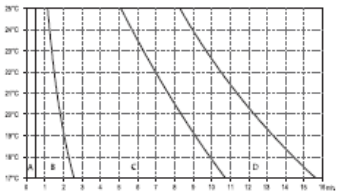
Safe disposal
1. Mixed cement should set before it is discarded with hospital waste.
2. For separate disposal of powder and liquid, please ask local waste disposal authorities.

Information
For further information, please contact your supplier or the manufacturer directly.

Symbol definitions

Manufacturer	Consult instructions for use
Use-by date	Caution
Batch code	CE marking of conformity
Catalogue number	Registered trademark
Sterilized using aseptic processing techniques	Flammable
Sterilized using ethylene oxide	Harmful
Do not resterilize	Health Hazard
Do not use if package is damaged	Ampoule
Keep away from sunlight	Blister
Temperature limit	Pouch
Do not re-use	

Fig. 1: Manual Mixing



A: Mixing phase
B: Waiting phase
C: Application phase
D: Hardening phase

Fig. 2: Vacuum Mixing [1]

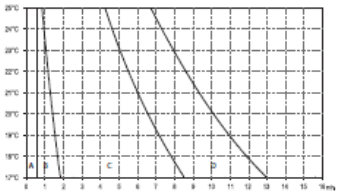
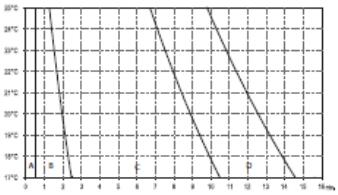


Fig. 3: Prechilled Vacuum Mixing [1]



[1] Different mixers may have different effects on the properties of the bone cement

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