SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Osseoanchored Prostheses for the Rehabilitation of Amputees (OPRA™)

Device Trade Name: OPRA™ Implant System

Device Procode: PJY

Applicant's Name and Address: Integrum AB
Krokslätts Fabriker 50,
SE-431 37 Mölndal, Sweden

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P190009

Date of FDA Notice of Approval: December 18, 2020

II. INDICATIONS FOR USE

The OPRA™ Implant System is indicated for patients who have transfemoral amputation due to trauma or cancer and who have or are anticipated to have rehabilitation problems with, or cannot use, a conventional socket prosthesis. The OPRA™ Implant System is intended for skeletally mature patients.

The patient failed to receive benefit from socket prostheses or is expected to not tolerate socket use due to problems such as:

- Recurrent skin infections and ulcerations in the socket contact area
- Pain
- A short stump preventing the use of socket prosthesis
- Volume fluctuation in the stump
- Soft tissue scarring
- Extensive area of skin grafting
- Socket retention problems due to excessive perspiration
- Restricted mobility

III. CONTRAINDICATIONS

The OPRA™ Implant System is not recommended for patients if any of the following is applicable:

- The patient's skeletal growth is not complete. Completed skeletal growth is defined through the finding of generally closed epiphyseal zones on X-ray.

- The patient has atypical skeletal anatomy which may affect treatment with OPRA™ Implant System. Examples of atypical skeletal anatomy:
  - Skeletal dimensions outside defined interval.
  - Development anomalies.
  - Conditions which are not amenable to device insertion such as deformities, fracture, infection.
- The patient would have less than 2 mm of remaining cortex bone available around the implant, if implanted.
- The patient has osteoporosis (weak bones).
- The patient is older than 65 years or younger than 22 years.
- The patient's body weight is higher than 220 lbs including the prosthesis.
- Do not treat patients with the following concurrent diseases:
  - Severe peripheral vascular disease.
  - Diabetic mellitus with complications.
  - Skin disorders involving the residual extremity.
  - Neuropathy or neuropathic disease and severe phantom pain.
  - Active infection or dormant bacteria.
  - Metabolic bone disease and/or metastatic lesions in the residual femur.
- The patient is pregnant.
- The patient is not expected to comply with treatment and follow up requirements.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the OPRA™ Implant System labeling.

V. DEVICE DESCRIPTION

The OPRA™ Implant System consists of an anchorage element (Fixture) and a skin-penetrating device (Abutment). The Fixture is surgically inserted in the medullary canal of the remaining femoral skeleton and, after a healing time of approximately six months, the Abutment is connected to the Fixture. The amputation prosthesis is then attached directly to the external part of the Abutment, via the OPRA™ Axor™ II. A list of component parts in the table below.

Component	Description
Fixture (Biohelix, Grade 5) 	A titanium screw that will anchor the artificial leg prosthesis to the femur.
Central Screw (Ridge)	A screw made of titanium that allows access to the bone without removing the Fixture.

Component	Description
	
Healing Cylinder 	A part made of titanium that prevents bone from growing into the Fixture opening where the Abutment will be placed during the second surgery. The Healing Cylinder is implanted during the first surgery and removed during the second surgery.
Washer 	A washer made of titanium that together with the Graft screw holds the bone graft in place. It is implanted during the first surgery and removed during the second surgery.
Graft Screw 	A titanium screw inserted into the Healing Cylinder that holds the bone graft in place. It is implanted during the first surgery and removed during the second surgery.
Abutment 	A titanium part that attaches to the Fixture and extends outside the skin to allow the attachment of the prosthesis. It is implanted during the second surgery.
Abutment Screw 	A screw made of titanium alloy that locks the Abutment to the Fixture. It is implanted during the second surgery.
Axor™ II	An external prosthetic connection device that provides a standard connection to other

Component	Description
	prosthetic components that would include the prosthetic knee and foot.

The OPRA™ Implant System is implanted in two surgical stages: Stage 1 (S1) and Stage 2 (S2). **Figures 1** and **2** show the components as implanted after the surgical stages.

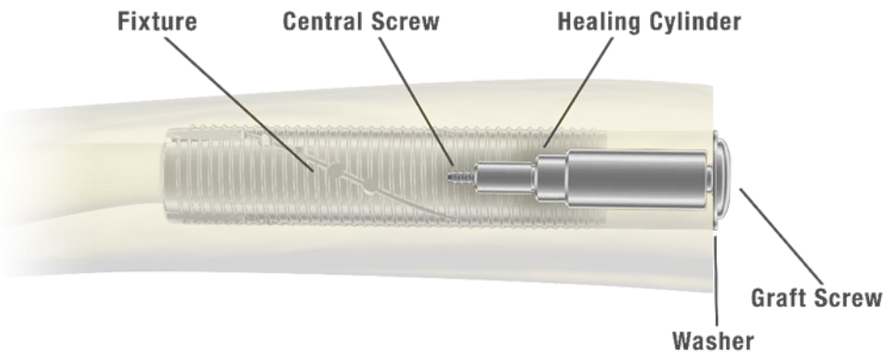

Figure 1. OPRA™ Implant System Parts Implanted in Stage 1 (S1).

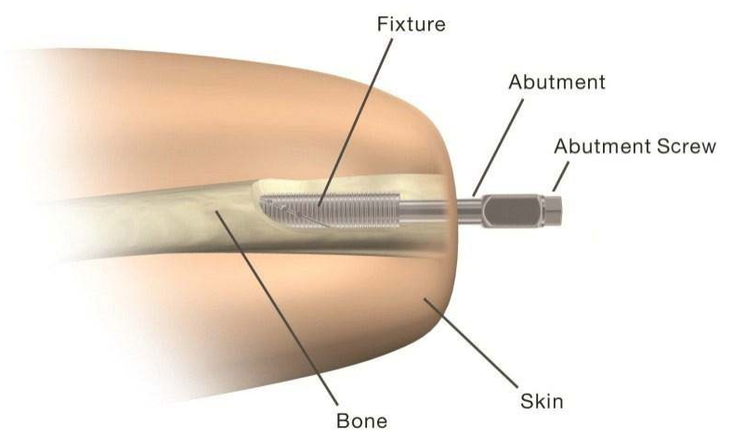

Figure 2. Abutment and Abutment Screw inserted in the Fixture during Stage 2 (S2) (superior cortex removed for visualization of the device).

The OPRA™ Axor™ II attaches to the Abutment end that is outside of the skin and acts as a safety connection between the Abutment and the prosthesis. It is designed to prevent damage to the bone-anchored Fixture if it is overloaded. If an overload occurs, the Axor™ II twists the prosthesis to protect the Fixture from damage.

The Axor™ II provides a standard connection to other prosthetic components that would include the prosthetic knee and foot. A standard European 4-hole male/female mounting system is utilized according to **Figure 3** below. This allows the OPRA™ Implant System to be connected to all prosthetic systems that utilize this standardized connection method.

The OPRA™ Implant System is intended for use with commercially available non-microprocessor controlled prosthetic knees and microprocessor controlled prosthetic knees that do not include powered activation of flexion and extension of the prosthetic knee.

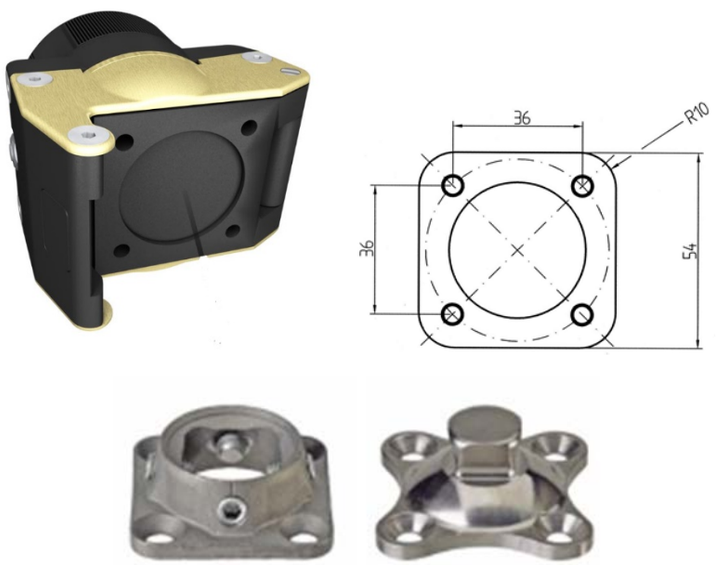

Figure 3. Pictures showing the standard European 4-hole interface prosthetic connection.

Figure 4 shows the OPRA™ Implant System and the Axor™ II with an amputation prosthesis attached on a person.

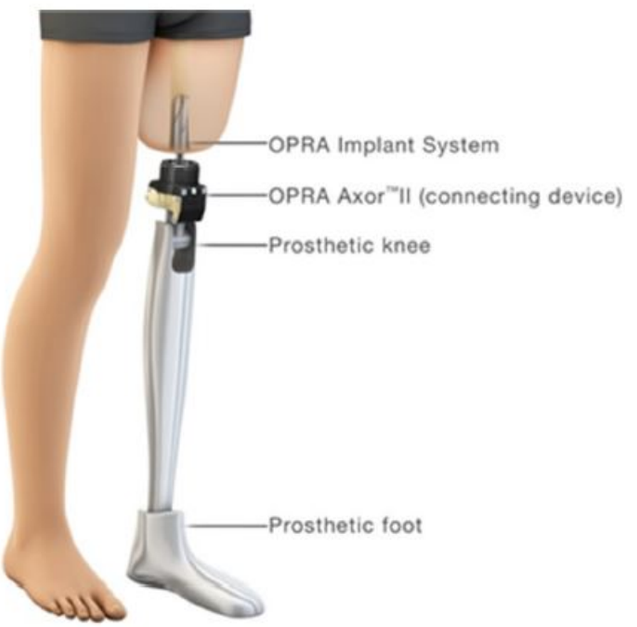

Figure 4. The OPRA™ Implant System, Axor™ II and Artificial Leg and Foot.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The rehabilitation of transfemoral amputees has traditionally been performed using socket prostheses; however, the indication for use for the OPRA™ Implant System is for patients who have or are anticipated to have rehabilitation problems with, or cannot use, a conventional socket prosthesis. For example, in some patients, the use of socket prostheses may lead to complications related to prosthesis retention and function, including inadequate retention, problems due to excessive perspiration, restricted mobility, soft tissue pain or scarring, skin ulcerations, and recurrent infections. In addition, socket prostheses are not an option for some amputees who have a short femur stump or volume fluctuations in the stump. If patients are unable to use socket prostheses, they may use crutches and/or wheelchairs, although these greatly restrict mobility.

VII. MARKETING HISTORY

The OPRA™ Implant System has been marketed outside of the United States as a custom made device since 1990 and CE marked since 2000. The OPRA™ Implant System has been, and/or currently is, distributed in the following countries: Austria, Australia, Belgium, Chile, Denmark, France, Italy, Jordan, Netherlands, Norway, Portugal, Spain, Sweden, and the United Kingdom. The OPRA™ Implant System has been marketed under a Humanitarian Device Exemption (HDE) marketing application in the U.S. since 2015. The OPRA™ Implant System has not been withdrawn from distribution/ marketing in any country for any safety or effectiveness reasons.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- Superficial infection
- Mechanical complication of abutment or abutment screw
- Pain
- Loosening of the fixture
- Deep infection
- Osteomyelitis (bone infection)
- Injury due to gait instability and/or falls
- Bone fracture
- Skin necrosis
- Pyrexia
- Soft tissue necrosis
- Chills
- Impaired healing
- Wound necrosis
- Joint injury
- Post procedural hematoma
- Myositis
- Blister
- Antibiotic toxicity from repeated administration
- Sepsis

For the specific adverse events that occurred in the primary clinical study, other clinical experience, and other literature studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Table 1. Laboratory Studies Overview

Test	Purpose	Method	Acceptance Criteria	Results
Laboratory Studies of OPRA™ Implant System Fixture and Abutment Components				
Bending Fatigue Testing	Validate sufficient mechanical strength for intended use life	Bending test where axial load translates into bending moment	Survive 10M cycles at 85 Nm 6 samples	Passed test with no crack initiation in any component.
Bending Fatigue Testing	Validate sufficient mechanical strength for intended use life	Rotation bending	Equal or better fatigue life at 60 Nm than OPRA™ 1.0 6 samples	Passed the test. OPRA™ 1.2 outperformed the fatigue life of OPRA™ 1.0 systems.

Test	Purpose	Method	Acceptance Criteria	Results
Torsion and Wear Fatigue Testing	Validate sufficient mechanical strength for intended use life in saline	Torsion test	Equal or better fatigue life at 5M cycles of ±15 Nm than OPRA™ 1.0 3 samples	Passed the test. OPRA™ 1.2 showed less wear than OPRA™ 1.0. Both systems fulfilled the requirement.
Torsion and Wear Fatigue Testing	Validate sufficient wear and corrosion resistance for intended use life in saline	Torsion test	Equal or better fatigue life at 10M cycles of ±15 Nm than OPRA™ 1.0 3 samples	Passed the test. OPRA™ 1.2 showed less wear than OPRA™ 1.0 after 10M cycles.
Laboratory and Simulated Use Studies to Support Changes since Original HDE Approval for the OPRA™ Implant System				
FEM Modeling for Material Change	Comparative analysis of stress gradients between possible new designs	Finite element analysis	Lower stress gradients than OPRA™ 1.0	Passed. Comparative stress gradients for OPRA™ 1.0 vs OPRA™1.2 confirmed the possible fatigue life improvement. Comparative analysis of OPRA™ 1.0 system with and without bone support confirmed the reduction in stress level in the presence of bone support.
Leakage Rate Testing	Validate sufficient leakage rate performance to meet performance requirement	Leakage test	Leakage rate less than 6 µl/min	Passed the test. The updated central screw with ridge design showed an average leakage rate 0.29 µL/min.
Healing Component Simulated Use Testing	Functional test of new healing components	Surgical procedure according to instructions for use/surgical technique	Positive clinical outcome at implantation and removal	Passed. The surgical team could verify functionality and performance during implantation and removal.
Laboratory Studies of Axor™ II OPRA™ Implant System Component				
Maximum Axial Testing	Structural integrity during rare events such as a fall	An axial load of 2700 N was applied via the Abutment.	No mechanical failure 6 samples	No failure was seen in the system.
Maximum Bend Testing	Structural integrity during rare events such as a fall	The Abutment was placed in the Axor™ II and 250 Nm moment was applied	No mechanical failure 6 samples	No failure was seen in the system.

Test	Purpose	Method	Acceptance Criteria	Results
		in lateral medial direction		
Torque release Testing	To confirm performance of the rotation release mechanism throughout use life.	The Axor™ IÍ was placed in a test setup that allowed for repeated rotation release through an application of a torsional moment. The release- and reset was performed 1500 times at 15 Nm.	The rotation release moment shall not change more than 15% after 1500 release cycles 6 samples	After the test, the rotation release moment had changed less than 15%.
Bend release Testing	To confirm performance of the bend release mechanism throughout use life.	The Axor™ IÍ was placed in a test setup that allowed for repeated bending release through an application of an axial force. The release and reset were performed 500 times at 70 Nm	The bend release moment shall not decrease more than 15% after 500 release cycles 6 samples	After the test, the bending release moment had changed less than 15%.
Fatigue test	To confirm mechanical strength of the Axor™ II throughout use life	Dynamic load test, which generates 80 Nm bending moment at a frequency of 5 Hz for 1M	No significant wear or deformation. 6 samples	Minimal wear and no deformation in the clamping function of the Axor™ II and the Abutment were observed. Devices passed maximum static tests after the fatigue test.

B. Additional Studies

Table 2. Additional Testing Overview

Test	Purpose	Test Method (*see all abbreviations below)	Results
Biocompatibility	Demonstrate that the OPRA™ Implant System is biocompatible.	ISO 10993-1	All patient contacting materials are biocompatible.
Stability	Shelf life determination	ASTM F1980-02 ISO 11607-1	Shelf life period of 2 years substantiated.

Test	Purpose	Test Method (*see all abbreviations below)	Results
Sterilization	Sterilization validation ensures the sterilization process is adequate	ISO 11137-1 and -2	SAL 10^{-6} was achieved.
Cleaning/Sterility of Reusable Components	Steam sterilization validation and cleaning validation	ANSI/AAMI ST79, AAMI TIR12, ANSI/AAMI/ISO 17665, USP<1211> AAMI TIR30:2011	SAL 10^{-6} was achieved. Cleaning methods sufficiently reduced soil on the instruments.
Magnetic Resonance Imaging (MRI) Testing	Demonstrate device safety in Magnetic Resonance (MR) environment	Displacement force and torque effects according to ASTM F2052-15 and ASTM F2213-17 RF Heating test according to ASTM F2182-19 Image artifacts at 3T according to ASTM F2119-07	The OPRA™ Implant System is MR Conditional. The MR system used to scan a patient should meet the following conditions: •Static Magnetic field of 1.5 and 3.0 T •Maximum spatial field gradient of 4500 gauss/cm (45 T/m) •Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (normal operation mode) when the implant is at least 20 cm out of isocenter. RF heating tests of the OPRA™ Implant System showed high expected temperature increase for a wbSAR of 2W/kg after 15 minutes of continuous scanning when at the isocenter. Moving the device 20 cm out of iso center, as listed in the conditions above, reduced heating to 3.9°C. The image artifact caused by the device extends approximately up to 45 mm from the OPRA™ Implant System when imaged with a gradient echo pulse sequence and a 3.0 T MRI system. It is likely that clinical MR protocols may show smaller artifacts.

* AAMI: Association for the Advancement of Medical Instrumentation
ANSI: American National Standards Institute
ASTM: ASTM, International
ISO: International Standardization Organization
USP: United States Pharmacopeia

X. SUMMARY OF PRIMARY CLINICAL STUDY

The OPRA™ Implant System was evaluated for safety and effectiveness from clinical study data of 65 participants.

Summary of the OPRA™ Implant System Clinical Investigation

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the OPRA™ Implant System for patients who have transfemoral amputation due to trauma or cancer and who have, or are anticipated to have rehabilitation problems with, or cannot use, a conventional socket prosthesis. Data from this clinical study and literature studies supported HDE approval in 2015 and were the basis for the PMA approval decision. For the PMA approval, a total of 65 subjects were analyzed, including 51 subjects from the primary clinical study with 14 additional subjects who were implanted at Sahlgrenska University Hospital, Gothenburg, Sweden between March 2007 and November 2011 with an OPRA™ implant very similar to the study implant, in principle only excluding the tantalum beads which does not affect clinical outcomes and met the same eligibility criteria as the OPRA™ study. Two and five-year outcomes are presented for the N=65 cohort.

The data with the 65 subjects presented below was obtained with an older version of the OPRA™ Implant System device. Since that time, the device has undergone incremental improvements for safety. Specifically, the Fixture, the Abutment, and the connection between the Fixture and Abutment have been redesigned with improved mechanical characteristics, both in fatigue and ultimate strength, leading to a stronger and more durable device. The safety device connection (the Axor™ II) between the Abutment and external prosthetic components has been further improved and adds control not only in torsion but also in bending.

A. Study Design

A prospective investigation was performed at Sahlgrenska University Hospital on transfemoral bone-anchored amputation prostheses. The study began in 1999. Each of the 51 subjects served as his/her own historical control, as the study was not randomized. Six of the 51 patients were bilateral subjects. The remaining forty-five patients were unilateral subjects. Due to the small sample size of the bilateral patients, this group was unable to be separated and studied alone. The length of the study was 2 years.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the prospective study was limited to patients who met the following inclusion criteria:

   - Transfemoral amputee patients with problems using a conventional socket prosthesis OR patients anticipated to experience significant problems with socket use
   - Undergone pre-operative Radiographic assessment including CT of the femur stump
   - Skeletal maturity
   - Normal retained femur anatomy
   - Body weight less than 100 kg (220 lb)
   - Suitable for surgery based on upon medical history and physical examination
   - Ability to comply with the rehabilitative and follow up regimen
     - Ability to give written Informed Consent

Patients were not permitted to enroll in the prospective study if they met any of the following exclusion criteria:

- Over 70 years of age
- Severe peripheral vascular disease, diabetes mellitus with complications, skin diseases involving the amputated limb or other diseases that could affect the suggested treatment negatively
- Systemically administrated corticosteroids, chemotherapy drugs or other drugs in a way that could affect the suggested treatment negatively
- Pregnant

2. Follow-up Schedule

Surgery was performed in two stages. The first to implant the OPRA™ Implant System fixture and the second to mount an abutment on which a safety coupling for the actual prosthesis could be attached. Visits were done at 3, 6, 12 and 24 months.

The Clinical Investigation consisted of 7 assessment visits. The multiple procedures performed at each visit (marked with X at each time point) are outlined in **Table 3**.

1. Pre-Operative Assessments.
2. Surgery Stage I Assessments.
3. Surgery Stage II Assessments.
4. Assessments 3 Months Post Surgery Stage II.
5. Assessments 6 Months Post Surgery Stage II.
6. Assessments 12 Months Post Surgery Stage II.
7. Assessments 24 Months Post Surgery Stage II.

Table 3. Study Assessments

ASSESSMENTS	PRE	S I	S II	3 M	6 M	12 M	24 M
PRE-OPERATIVE: · ELIGIBILITY CHECKLIST · SUBJECT DETAILS · RADIOGRAPHY · COMPUTED TOMOGRAPHY · MEDICATION · PRE-OP HIP JOINT MOTION · PRE-OP QUESTIONNAIRES · PCI · STRENGTH · REGISTRATION OF EXTERNAL COMPONENTS · VIBRAMETRY	X						
SURGERY STAGE I: · SURGERY DETAILS · POST-OP CLINICAL DETAILS · POST-OP RADIOGRAPHY · POST-OP RSA · MEDICATION		X					
SURGERY STAGE II: · PRE-OP RADIOGRAPHY · SURGERY DETAILS · POST-OP CLINICAL DETAILS · POST-OP RADIOGRAPHY · POST-OP RSA · 3 WEEKS POST-OP CLINICAL ASSESSMENT · MEDICATION			X				
POST-OP STAGE II – 3 AND 6 MONTHS: · CLINICAL ASSESSMENT · RADIOGRAPHY · RSA · MEDICATION · REHABILITATION DETAILS				X	X		

ASSESSMENTS	PRE	S I	S II	3 M	6 M	12 M	24 M
POST-OP STAGE II–12 AND 24 MONTHS: · CLINICAL ASSESSMENT · RADIOGRAPHY · RSA · MEDICATION · REHABILITATION DETAILS · POST-OP HIP JOINT MOTION · POST-OP QUESTIONNAIRES · PCI · STRENGTH · REGISTRATION OF EXTERNAL COMPONENTS · VIBRAMETRY						X	X
ADVERSE EVENTS	When applicable	When applicable	When applicable	When applicable	When applicable	When applicable	When applicable
REOPERATION		When applicable	When applicable	When applicable	When applicable	When applicable	When applicable
COMPLETION / WITHDRAWAL	When applicable	When applicable	When applicable	When applicable	When applicable	When applicable	X

S: surgery; M: month.

Following the original 2-year study, patients were followed for an extended period of time after Surgery Stage II. Five-year outcomes for a subset of patients are summarized further below.

3. Clinical Endpoints

The primary effectiveness endpoint of the original clinical investigation was to evaluate the improvement of Prosthetic Use Score captured by the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA), a patient reported outcome measure, comparing the OPRA™ Implant System to baseline (i.e., to socket prosthesis).

The primary safety endpoint was time to revision defined as removal of fixture and removal of abutment. Infection, reoperation, and other safety data were also collected.

The secondary effectiveness endpoints included the Q-TFA problem, mobility, and global sub-scales and individual questions regarding time usage of the prosthesis per week. The SF-36 (i.e., Short Form (36) Health Survey, which is a 36-item, patient-reported survey of patient health) was also included.

B. Accountability of OPRA™ Clinical Study Cohort

The accounting of the subjects over the duration of the study in the Intent-to-Treat (ITT) population is presented below in **Table 4**.

Table 4. Subject Accountability, ITT Population

	Baseline	12 months	24 months
Theoretical [1]	51	51	51
Deaths [2]	0	1	1
Failures [3]	0	1	4
Expected [4]	51	49	46
Actual[A]	47	42	36
% Follow-up [5]	92.2	85.7	78.3
Actual[B]	51	47	45
% Follow-up [6]	100.0	95.9	97.8

NA: Not applicable
Actual[A]: Subjects with complete data for each endpoint, evaluated per protocol, in the window of time.
Actual[B]: Subjects with any follow-up data reviewed or evaluated by the investigator ("all evaluated" accounting).
[1] Number of subjects that would have reached the beginning of the study window associated with each visit if all subjects returned.
[2] Cumulative number of subjects that died during or prior to the study visit.
[3] Cumulative number of subjects that failed (Fixture revision) during or prior to the study visit.
[4] Theoretical subjects minus the number of deaths and revisions.
[5] Actual[A]/Expected*100
[6] Actual[B]/Expected*100

Missing is defined as lack of data for any reason, e.g. visit not done, data not captured during a visit or subject lost to follow-up.

C. Study Population Demographics and Baseline Parameters

The subjects' demographics and baseline characteristics for the ITT population are presented in **Table 5** below. The study enrolled 28 males (55%) and 23 females (45%) with a mean age of 44.2 years and mean Body Mass Index (BMI) of 28.1 kg/m^2.

The major reason for amputation was trauma in 33 (65%) followed by tumor in 12 (24%) of the subjects. Six (12%) of the subjects had vascular disease or other reason for the amputation.

Forty-two (82%) of the subjects were using socket prosthesis at enrollment, and 8 (16%) had been using a socket prosthesis at some point prior to enrollment. In addition, one patient (2%) was a bilateral amputee who never used a socket prosthesis because of very short stumps. Data from baseline may therefore be considered a comparison to socket prosthesis. The mean time between amputation and surgery stage I in the study was 12.1 years. Eleven (22%) of the subjects were smokers at inclusion.

About half of the subjects were using concomitant medication at study start.

Table 5. Subject Demographics and Baseline Characteristics (ITT Population)

Variable	ITT Population (n=51)
Gender	
Male	28 (54.9%)
Female	23 (45.1%)
Age at inclusion (years)	44.2 (12.2) 46.4 (19.9; 64.7) n=51
Unilateral/bilateral amputated	
Unilateral	45 (88.2%)
Bilateral	6 (11.8%)
Reason for amputation	
Trauma	33 (64.7%)
Peripheral Vascular Disease	2 (3.9%)
Tumor	12 (23.5%)
Other	4 (7.8%)
Time between amputation and surgery SI (years)	12.1 (11.1) 8.0 (0.9; 41.8) n=51
Age at amputation (years)	32.4 (13.6) 31.6 (13.0; 63.8) n=50
Estimated weight at inclusion (kg)[1]	83.5 (18.6) 83.4 (50.4; 128.8) n=50
Height at inclusion (cm)	172.4 (10.2) 173.5 (154.0; 194.0) n=48

Variable	ITT Population (n=51)
Estimated BMI at inclusion (kg/m^2)[2]	28.1 (4.9) 26.9 (17.4; 42.1) n=48
Smoker at inclusion	11 (21.6%)
Prosthetic user at inclusion	42 (82.4%)
Ever used prosthesis if not Prosthetic user at inclusion	8 (88.9%)[3]
Level of education	
Primary school	11 (23.9%)
Secondary school	23 (50.0%)
Exam from University	12 (26.1%)
Data missing	5
Civil status	
Single	19 (37.3%)
Married/cohabiting	32 (62.7%)
Nationality	
England	1 (2.0%)
Norway	14 (27.5%)
Spain	11 (21.6%)
Sweden	25 (49.0%)
Employment at inclusion (%)	35.1 (41.7) 10.0 (0.0; 100.0) n=51
Medication at inclusion	
Yes	26 (51.0%)
No	25 (49.0%)

For categorical variables n (%) is presented.

For continuous variables Mean (SD) / Median (Min; Max) / n= is presented.

[1] Weight has been measured without prosthesis. For unilateral patients, 12% have been added to calculate the estimated weight, and for bilateral, approximately 27.3% have been added.

[2] The estimated BMI is based on estimated weight and height. Height is measured with prosthesis.

[3] One observation is missing. The patient was a bilateral amputee who never used a socket prosthesis because of very short stumps. However, one of the limbs was long enough to be treated with the OPRA™ Implant System and the patient was using a bone-anchored prosthesis. The treatment was performed only 10 months after amputation.

D. Safety and Effectiveness Results

1. Safety Results

Adverse effects that occurred in the primary clinical study:

Adverse Events (AEs) were captured from the enrollment of the subject and until the subject had the 24-month visit. Five-year safety data for a subset of patients are presented further below.

An AE was defined as any undesirable clinical occurrence in a subject whether it was considered to be related to the OPRA™ Implant System or not. All AEs during the study were to be recorded. An AE could be both objective and subjective. The primary Safety variable was time to revision. Adverse events were captured as the following:

- Onset of Adverse Event
- Expected AEs
  - Superficial Infection
  - Deep Infection
  - Pain
  - Mechanical complication of OPRA™
  - Skeletal fracture
  - Loosening of OPRA™
- Unexpected AEs
- Severity of Adverse Event

The AEs were classified as mild, moderate or severe with respect to their intensity. The following definitions were used:

- Mild: AE which was easily tolerated
- Moderate: AE which causes sufficient discomfort to interfere with daily activities
- Severe: AE which caused marked limitation in activity, some assistance may have been needed, medical intervention/therapy required, hospitalization was possible

The AEs were evaluated for seriousness. A Serious Adverse Event (SAE) was defined as any untoward medical occurrence that:

- Resulted in death
- Was life-threatening
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity

The relationship to the OPRA™ Implant System was classified as:

- Not related: The Adverse Event was definitely not related to the OPRA™ Implant System

- Probably Unrelated: Cause and effect relationship between the AE and OPRA™ Implant System was not demonstrated, was improbable, but not impossible
- Possibly Related: A direct cause and effect relationship between the AE and the OPRA™ Implant System was not demonstrated, but is possible or likely
- Related: There is a direct cause and effect relationship between the AE and the OPRA™ Implant System.

Early loosening was the most common adverse event requiring surgical removal of the OPRA™ Implant System and removal was normally performed within the first two years after the Stage 2 surgery. No implant fracture was reported with the OPRA™ Implant System. In no subject, regardless of adverse event, was it necessary to revise the femoral bone by resecting further proximally thereby shortening the femur.

There was a total of 101 treatment emergent AEs. **Table 6** summarizes all adverse events that were either related or possibly related to use of the OPRA™ device. The most frequent AEs related to the treatment during the 2-year study were:

- Infection: 31 (61%) subjects with 44 events
  - Superficial infection: 28 (55%) subjects with 40 events
  - Deep infection: 3 (6%) subjects with 4 events
- Mechanical complication of the implant: 4 (8%) subjects with 9 events
- Pain: 6 (12%) subjects with 6 events
- Injury: 4 (8%) subjects with 4 events
- Loosening of the Fixture: 4 (8%) subjects with 4 events

Table 6. Treatment Emergent Related and Possible Related Adverse Events (Safety Population)

System Organ Class PT	Safety Population (n=51)	
	AEs	Total Subjects with AEs n (%)
Any AE	**84**	**44 (86.3%)**
General disorders and administration site conditions	**20**	**12 (23.5%)**
Chills	1	1 (2.0%)
Impaired healing	1	1 (2.0%)
Mechanical complication of implant	9	4 (7.8%)
Pain	6	6 (11.8%)
Pyrexia	2	2 (3.9%)
Wound necrosis	1	1 (2.0%)
Infections	**44**	**31 (60.8%)**
Superficial	40	28 (54.9%)
Deep	4	3 (5.9%)
Injury, poisoning and procedural complications	**13**	**13 (25.5%)**
Loosening of the fixture resulting in device removal/failure	4	4 (7.8%)
Skeletal fracture	3	3 (5.9%)
Injury*	4	4 (7.8%)
Joint injury	1	1 (2.0%)
Post procedural hematoma	1	1 (2.0%)
Musculoskeletal and connective tissue disorders	**3**	**3 (5.9%)**
Myositis	1	1 (2.0%)
Soft tissue necrosis	2	2 (3.9%)
Skin and subcutaneous tissue disorders	**4**	**4 (7.8%)**
Blister	1	1 (2.0%)
Skin necrosis	3	3 (5.9%)

* 4 events of trauma resulting from falls

As noted above, 28 subjects experienced a superficial infection. Three subjects experienced a deep infection. In the study, none of the superficial infections developed into a deep infection; no patient who developed a deep infection had a previous superficial infection.

Among the 84 treatment emergent related and possibly related AEs, the most frequent SAEs were:

- Superficial infection, 4 (7.8%) subjects with 4 (4.8%) events,
- Deep infection, reported by 3 (5.9%) subjects with 4 (4.8%) events, and

- Secondary surgical intervention (including reoperation, component replacement/revision, removal): 13 (15.5%) events reported by 13 (25.5%) subjects; of the 13 events, 4 (4.8%) events reported by 4 (7.8%) subjects were specific to implant (fixture) removal (3 implants removed during the study and 1 shortly after the study, giving 4 events in 4 patients).

Table 7 shows the distribution of subjects with treatment emergent adverse events for the different time periods throughout the study. This table shows the number of subjects with treatment emergent adverse events whether or not they were deemed to be related, possibly related, or not related to the OPRA™ Implant System. Please note, **Table 7** shows 'subjects with events' at each time point; therefore, one subject may be represented multiple times in the table if they experienced an adverse event at more than one time point. However, as **Table 7** counts 'subjects with events', not 'total events', if a subject had multiple events occur within one time period, it would only be captured once. Please also note, all adverse events listed in **Table 6** are captured in **Table 7**; however, they are categorized differently, such that major adverse events, such as infection, pain and loosening are called out; while, minor events, such as chills or bruising, are captured as other.

Table 7. Subjects with Treatment Emergent Adverse Events over Time

	Immed. Post-op Surgery 1 (n=51)	**After Immed. Post-op Surgery 1 – Surgery 2 (n=51)**	**Immed. Post-op Surgery 2 (n=51)**	**After Immed. Post-op Surgery 2 – 3 months (n=51)**	**3 months – 6 months (n=51)**	**6 months – 12 months (n=48)**	**12 months – End of Study (n=48)**
	Subjects with Events n (%)	**Subjects with Events n (%) ×None**	**Subjects with Events n (%)**	**Subjects with Events n (%)**	**Subjects with Events n (%)**	**Subjects with Events n (%)**	**Subjects with Events n (%)**
Operative Site Events							
Superficial Infection			6 (11.8%)	3 (5.9%)	4 (7.8%)	13 (27.1%)	12 (25.0%)
Deep Infection	2 (3.9%)		3 (5.9%)				
Pain					1 (2.0%)	3 (6.3%)	3 (6.3%)
Onset of loosening of OPRA™ Implant System			1 (2.0%)			3* (5.5%)	
Skeletal fracture				1 (2.0%)		2 (3.9%)	1 (2.1%)
Trauma					2 (3.9%)	2 (3.9%)	3 (6.3%)
Mechanical complication of OPRA™ Implant System						1 (2.1%)	4 (8.3%)
Systemic Events							

	Immed. Post-op Surgery 1 (n=51)	**After Immed. Post-op Surgery 1 – Surgery 2 (n=51)**	**Immed. Post-op Surgery 2 (n=51)**	**After Immed. Post-op Surgery 2 – 3 months (n=51)**	**3 months – 6 months (n=51)**	**6 months – 12 months (n=48)**	**12 months – End of Study (n=48)**
	Subjects with Events n (%)	**Subjects with Events n (%) ˣNone**	**Subjects with Events n (%)**	**Subjects with Events n (%)**	**Subjects with Events n (%)**	**Subjects with Events n (%)**	**Subjects with Events n (%)**
Myocardial infarction ˣNone							
Pulmonary emboli ˣNone							
Urinary tract infection						1 (2.1%)	
Other	3 (5.9%)		6 (11.8%)	1 (2.0%)	2 (3.9%)	4 (8.3%)	4 (8.3%)

Immediately Post-op Surgery is defined within 42 days.
* 1 patient showed signs of loosening of OPRA™ within the study, but the fixture was removed 4 months after the 24 month follow-up
ˣNone: The grey cells denote that no events were reported in these categories.

2. Effectiveness Results

For the primary endpoint, the mean prosthetic use score at baseline was 46.7 (standard deviation or SD: 36.7) out of 100. The score increased significantly, from baseline to 12 months, mean score 79.7 (22.7) and was sustained at 24 months, mean score 79.9 (27.1) ($p<0.0001$) **(Table 8**). The OPRA™ Implant System was also able to provide subjects with benefits such as longer walking distances, easier attachment and de-attachment of the prosthesis and increased sitting comfort.

Cumulative survival rate of the Fixture (defined as lack of Fixture removal or revision) after two years of follow up was 92% in terms of patient survival and 93% in terms of implant survival. This calculation was based on standard Kaplan-Meier curves and the fact that four patients were treated bilaterally who have two implants/fixtures (i.e., for a total of 51 patients, 55 implants were used, and four patients had a fixture removal) with an assumption that non-observed data is non-informative.

Table 8. Primary Effectiveness Analysis: Q-TFA derived Prosthetic Use Score (ITT Population)

				Change from Baseline to 12 months		Change from Baseline to 24 months	
Variable	**Baseline (n=51)**	**12 months (n=48)**	**24 months (n=45)**		**p-value**		**p-value**
Prosthetic Use score	46.7 (36.7) 52.0 (0.0; 100.0) n=51	79.7 (22.7) 90.0 (6.0; 100.0) n=44	79.9 (27.1) 90.0 (0.0; 100.0) n=45	34.4 (29.0) 29.0 (-23.0; 100.0) n=44	<0.0001	32.0 (41.0) 29.0 (-100.0; 100.0) n=45	<0.0001
For continuous variables Mean (Standard Deviation) / Median (Min; Max) / n= is presented. For comparison over time Wilcoxon Signed Rank test was used for continuous variables. Note: In terms of effectiveness, higher score is expected for the Prosthetic Use score.							

The average of the Q-TFA prosthetic use score stratified by baseline score and the changes in scores at 12 and 24 months are shown in **Figure 5**. As shown, low prosthetic users (baseline score <25) saw a large increase in prosthetic use at 1 and 2 years. The moderate prosthetic users (baseline scores 25-75) saw a slight increase and the high functional prosthetic users (baseline score >75) saw a slight decrease.

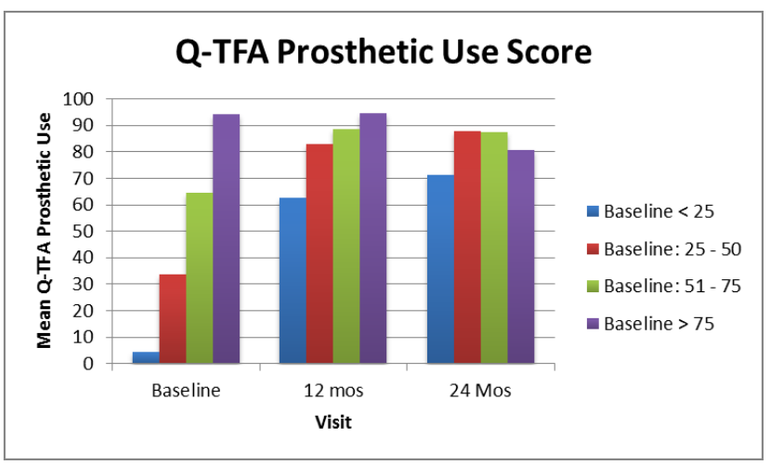

Figure 5. Mean Q-TFA Prosthetic Use Score by Visit.

Figure 6 shows the daily and weekly usage of the prosthetic device at baseline, 12 months and 24 months. As shown, the number of subjects using their prostheses increased during the study, both on an hourly and daily basis.

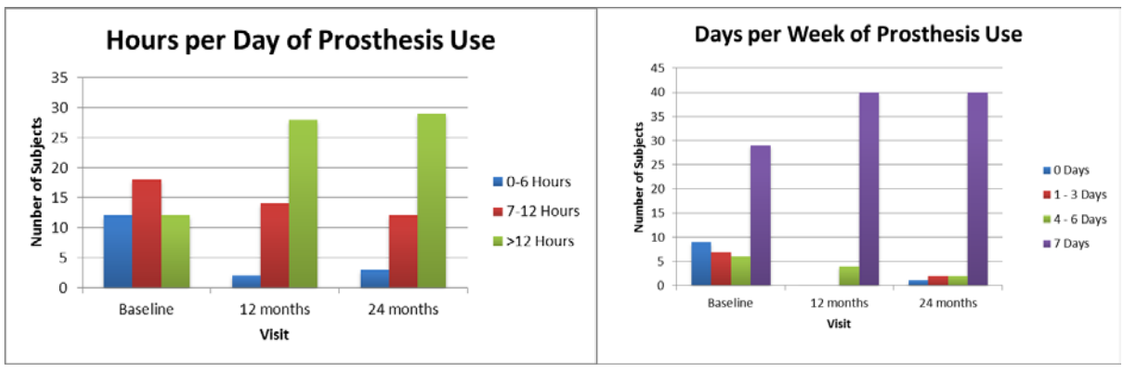

Figure 6. Prosthesis Use by Visit.

The following scores changed statistically significantly ($p<0.0001$) from baseline to the follow-up visits:

- The problem score decreased from baseline to 12 and to 24 months.
- The prosthetic mobility score, the walking habits sub-score, the capability sub-score and the global score increased from baseline to 12 and to 24 months.

There was no statistically significant change from baseline to 12 and 24 months in the walking aids subscore, though numerical improvements were observed. The Q-TFA secondary effectiveness variables are presented below in **Table 9**.

Table 9. Q-TFA Subscales

				Change from Baseline to 12 months		Change from Baseline to 24 months	
Variable	**Baseline (n=51)**	**12 months (n=48)**	**24 months (n=45)**		**p-value**		**p-value**
Problem Score	43.9 (18.7) 47.5 (5.0; 77.0) n=42	15.2 (10.0) 13.0 (2.0; 48.0) n=42	16.8 (12.3) 13.5 (1.0; 54.0) n=44	-28.4 (16.2) -33.0 (-57.0; 2.0) n=36	<0.0001	-26.6 (16.3) -30.0 (-59.0; 7.0) n=37	<0.0001
Prosthetic Mobility Score	52.5 (20.4) 56.0 (0.0; 82.0) n=42	60.0 (23.3) 64.5 (0.0; 91.0) n=44	64.1 (21.7) 71.0 (4.0; 91.0) n=44	14.0 (16.8) 15.0 (-29.0; 46.0) n=36	<0.0001	17.6 (15.6) 17.0 (-29.0; 48.0) n=37	<0.0001
Walking Habits (Subscore)	34.5 (19.2) 32.5 (0.0; 75.0) n=42	47.3 (22.6) 50.0 (0.0; 80.0) n=43	47.8 (23.9) 55.0 (0.0; 85.0) n=44	16.5 (16.9) 20.0 (-20.0; 50.0) n=36	<0.0001	18.8 (20.3) 15.0 (-20.0; 70.0) n=37	<0.0001

				Change from Baseline to 12 months		Change from Baseline to 24 months	
Variable	**Baseline (n=51)**	**12 months (n=48)**	**24 months (n=45)**		**p-value**		**p-value**
Walking Aids (Subscore)	73.4 (25.9) 83.0 (33.0; 100.0) n=39	66.5 (24.4) 75.0 (17.0; 100.0) n=40	71.6 (24.5) 83.0 (17.0; 100.0) n=40	-2.13 (26.70) 0.00 (-67.00; 50.00) n=32	0.5223	2.06 (21.18) 0.00 (-67.00; 50.00) n=33	0.4506
Capability (Subscore)	53.4 (23.5) 58.0 (0.0; 92.0) n=42	70.4 (29.2) 83.0 (0.0; 100.0) n=45	76.7 (23.6) 83.0 (8.0; 100.0) n=44	23.6 (24.9) 25.0 (-75.0; 75.0) n=37	<0.0001	27.9 (17.4) 25.0 (-25.0; 59.0) n=37	<0.0001
Global Score	37.7 (19.3) 33.0 (0.0; 92.0) n=42	73.6 (18.9) 75.0 (8.0; 100.0) n=42	75.0 (19.3) 75.0 (25.0; 100.0) n=44	37.3 (25.5) 34.0 (-17.0; 84.0) n=36	<0.0001	38.8 (24.3) 34.0 (0.0; 92.0) n=37	<0.0001

For continuous variables Mean (SD) / Median (Min; Max) / n= is presented.

For comparison over time Wilcoxon Signed Rank test was used for continuous variables.

Note: In terms of effectiveness, lower scores are expected for the Problem Sub-score, while higher scores are expected for the Prosthetic Mobility, Walking Habits, Capability, and Global Sub-scores.

With respect to the SF-36 questionnaire, statistically significant increases from baseline to 12 months and to 24 months were found for

- Physical Function ($p<0.0001$ for both 12 and 24 months)
- Role-Physical ($p=0.0004$ for 12 months and $p<0.0001$ for 24 months)
- Physical Component Summary ($p<0.0001$ for both 12 and 24 months)

Bodily pain, general health, vitality, social functioning, role-emotional, mental health, mental component summary and SF-36 first question "health in general" did not change significantly from baseline to either 12 or 24 months in the ITT population.

Furthermore, range of movement around the hip joint improved, physiological cost decreased, and abduction/adduction increased between baseline and 24 months.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included one principal investigator, two co-investigators, and two physiotherapists for rehabilitation assessments, none of whom were full-time or part-time employees of the sponsor and none had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study;
- Significant payment of other sorts;
- Proprietary interest in the product tested by the investigator; or
- Significant equity interest held by investigator in sponsor of covered study.

FDA also previously reviewed the OPRA™ Implant System and associated financial disclosures as part of the HDE submission and determined that the information provided did not raise questions about the reliability of the data.

F. Additional Analyses of OPRA™ Study with Additional Patients

As noted above, for PMA approval, 51 subjects from the primary clinical study used for HDE approval were analyzed with 14 additional subjects who had stage 1 surgery with the OPRA™ implant at Sahlgrenska University Hospital between March 2007 and November 2011 and met the same eligibility criteria as the primary clinical study. A summary of these analyses is below.

1. Baseline and Demographics Characteristics for Additional 14 Subjects

Table 10 presents baseline and demographic characteristics for the 14 additional subjects. The 14 subjects had similar characteristics to the original 51 OPRA™ study patients with the exception that 100% of the additional 14 subjects were male as compared to the 55%/45% male/female ratio in the original 51 subjects.

Table 10: Baseline and Demographic Characteristics for Additional 14 Subjects

Variable	14 Additional Patients
Gender	
Male	14 (100.0%)
Age at amputation (years)	36.1 (13.0) 33.5 (20; 58) n=14
Reason for amputation	
Trauma	11 (78.6%)
Peripheral Vascular Disease	0 (0.0%)

Variable	14 Additional Patients
Tumor	1 (7.1%)
Other	2 (14.3%)
Age at inclusion (years)	45.8 (11.7) 47.5 (27; 63) n=14
Estimated weight at inclusion (kg)	76.8 (12.5) 77 (55; 100) n=14
Height at inclusion (cm)	178.0 (5.8) 177 (170; 190) n=14
Smoker at inclusion	3 (21.4%)
Prosthetic user at inclusion	12 (92.3%)
Level of education	
Primary school	1 (20.0%)
Secondary school	3 (60.0%)
Exam from University	1 (20.0%)
Missing	9
Civil status	
Single	1 (12.5%)
Married/cohabiting	7 (87.5%)
Missing	6
Nationality	
Sweden	8 (57.1%)
Norway	4 (28.7%)
Spain	1 (7.1%)
Italy	1 (7.1%)
Medication at inclusion	
No	3 (25.0%)
Yes	9 (75.0%)
Missing	2
For categorical variables n (%) is presented. For continuous variables Mean (SD) / Median (Min; Max) / n= is presented.	

2. Endpoints

For the analysis with 65 subjects, new co-primary safety and effectiveness endpoints combined into a composite overall success endpoint, thus the composite primary endpoint is rate of overall success (i.e., success in both the primary effectiveness and safety endpoints).

With regard to success/failure criteria, the primary endpoint used to determine individual success is:

- Primary safety endpoints:
  - At 2 years: No subsequent secondary surgical interventions and at most 2 superficial infections.
  - At 5 years: No subsequent secondary surgical interventions and at most 3 superficial infections.

- Primary effectiveness endpoints: Patients achieved the minimally clinically important difference (MCID) for the total Q-TFA score (mean of all subscores, i.e., prosthetic use score, prosthetic mobility score, problem score, and global score) of 20.25 points* and radiographic success. Radiographic success was defined as "no radiographic loosening of the implant with a radiolucent zone wider than the thread depth surrounding the entire implant". These endpoints were measured 2 and 5 years after the stage 2 surgery.

Rates of overall success and overall no success (not achieving success in both primary safety and effectiveness) at 2 and 5 years were provided. Proportion of patients who achieved either primary safety endpoints or primary effectiveness endpoints at 2 and 5 years was also assessed, respectively. These analyses included imputations for patients with missing data.

Secondary endpoint: Proportion of patients who achieved the MCID for the Q-TFA Prosthetic Use subscore (19 points*), Prosthetic Mobility subscore (11 points*), Problem subscore (-23 points*) and Global subscore (33 points*), individually.

*The MCIDs for change from baseline for the Q-TFA subscales were derived individually and totally by the applicant using the validated SF-36 physical function subscore in a relevant population as an anchor (Escobar et al. (2007) and Keurentjes et al. (2012)).

3. Results

Table 11 presents the results of the primary effectiveness endpoints with 65 subjects. The data below demonstrates a high proportion of patients with effectiveness success at both time points (70.8% at 2 and 5 years), supporting the device's benefits to patients.

Table 11: Primary Effectiveness Results (Total Q-TFA and Radiographic Success)

Variable	Total (n=65)
Primary effectiveness endpoint: Total Q-TFA ⩾ MCID and radiographic success (2 years)	
Success	46 (70.8%)
Not Success	19 (29.2%)

Variable	Total (n=65)
Primary effectiveness endpoint: Total Q-TFA ⩾ MCID and radiographic success (5 years)	
Success	46 (70.8%)
Not Success	19 (29.2%)
For categorical variables n (%) is presented.	

The additional 14 subjects had a total of 30 treatment related adverse events including 23 surgical interventions, 20 mechanical complications, 2 deep infections, and 6 superficial infections. The surgical interventions addressed the mechanical complications and/or deep infections.

Table 12 presents the results of the primary safety endpoint with 65 subjects. At 2 years, 67.7% of patients met the safety endpoint and at 5 years, 43.1% of patients met the safety endpoint. The applicant used the safety criteria outlined above for the analysis with 65 subjects, but the rate of patients without success should be interpreted cautiously as patients who are technically not successful still derive clinical benefit from the device. For example, an uncontrolled fall not related to the device causes a high bending moment on the device and the bone. The device protects the bone from fracture by plastic deformation of the abutment and thereby absorbs energy from the fall and avoids a bone fracture. A femoral bone fracture, which can happen also in socket users, is typically treated with a major surgical intervention and up to 6 months of restricted loading. A bent abutment, however, is replaced under local anesthesia in less than 30 minutes and directly postoperatively, the patient can ambulate without restrictions. However, from a strict safety analysis perspective, this patient would be considered not to be successful under this safety endpoint. Thus, these values should be interpreted with caution as they do not take into account the design intent of the device into account.

Table 12: Primary Safety Results

Variable	Total (n=65)
Primary safety endpoint (2 years)	
Success	44 (67.7%)
Not Success	21 (32.3%)
Primary safety endpoint (5 years)	
Success	28 (43.1%)
Not Success	37 (56.9%)
For categorical variables n (%) is presented.	

Table 13 presents rates for overall success at 2 and 5 years. As shown, 47.7% and 35.4% were overall successes at 2 and 5 years, respectively. Notably, only 9.2% and 21.5% did not achieve both effectiveness and safety success at 2 and 5 years, respectively. Thus, at 2 years, 90.8% of patients had some level of success, whether effectiveness, safety, or both. The same is true for 78.5% of patients at 5 years.

Table 13: Overall Success

Variable	Total (n=65)
2 years	
Overall success	31 (47.7%)
Overall not success	6 (9.2%)
Primary safety success and no primary effectiveness success	13 (20.0%)
Effectiveness success and no primary safety success	15 (23.1%)
5 years	
Overall success	23 (35.4%)
Overall not success	14 (21.5%)
Primary safety success and no primary effectiveness success	5 (7.7%)
Effectiveness success and no primary safety success	23 (35.4%)
For categorical variables n (%) is presented.	

The applicant also provided additional data with SF-36 and Q-TFA for the 65 subjects, as presented below.

Table 14 presents changes in the SF-36 variables from before treatment to two and five years after treatment for the 65 subjects. As shown, there are statistically significant improvements across most SF-36 subscores two- and five-years post surgery.

Table 14: Change in SF-36 Variables from before Treatment to 2 Years and 5 Years

	Change from before treatment to 2 years (n=65)		Change from before treatment to 5 years (n=65)	
Variable		p-value within group		p-value within group
Physical Function	23.6 (20.2) 25 (-30; 75) (18.4; 28.8) n=62 SRM=1.17 ES=1.11	<0.0001	26.2 (23.1) 25 (-38.1; 85) (20.3; 32.1) n=61 SRM=1.13 ES=1.22	<0.0001
Role Physical	23.0 (41.8) 18.9 (-100; 100) (12.4; 33.5) n=62	0.0002	17.8 (54.2) 0 (-100; 100) (4.0; 31.8) n=61	0.014

	Change from before treatment to 2 years (n=65)		Change from before treatment to 5 years (n=65)	
	SRM=0.55 ES=0.56		SRM=0.33 ES=0.43	
Bodily Pain	12.4 (36.4) 10 (-74; 100) (3.1; 21.6) n=62 SRM=0.34 ES=0.46	0.0090	8.17 (32.14) 10 (-69; 90) (-0.11; 16.45) n=61 SRM=0.25 ES=0.30	0.054
General Health	1.40 (18.09) 0 (-42; 52.99) (-3.20; 5.97) n=62 SRM=0.08 ES=0.08	0.55	5.18 (21.57) 5 (-55; 61.65) (-0.39; 10.68) n=61 SRM=0.24 ES=0.30	0.068
Vitality	6.44 (25.62) 5 (-70; 70) (-0.14; 12.95) n=62 SRM=0.25 ES=0.30	0.055	6.81 (23.56) 5 (-55; 70) (0.85; 12.79) n=61 SRM=0.29 ES=0.32	0.023
Social Function	6.66 (30.92) 0 (-100; 87.5) (-1.16; 14.42) n=62 SRM=0.22 ES=0.26	0.096	7.47 (32.62) 0 (-62.5; 87.5) (-0.76; 15.79) n=61 SRM=0.23 ES=0.29	0.074
Role Emotional	4.77 (50.44) 0 (-100; 100) (-8.18; 17.50) n=62 SRM=0.09 ES=0.11	0.48	5.25 (46.17) 0 (-100; 100) (-6.63; 17.02) n=61 SRM=0.11 ES=0.12	0.39
Mental Health	4.99 (24.40) 8 (-76; 48) (-1.20; 11.10) n=62 SRM=0.20 ES=0.25	0.11	4.23 (22.54) 4 (-56; 52) (-1.57; 9.96) n=61 SRM=0.19 ES=0.21	0.15

	Change from before treatment to 2 years (n=65)		Change from before treatment to 5 years (n=65)	
Physical Composite	8.80 (10.03) 9.87 (-14.22; 29.83) (6.23; 11.36) n=62 SRM=0.88 ES=1.05	<0.0001	8.76 (10.76) 8.27 (-12.6; 37.04) (6.03; 11.49) n=61 SRM=0.81 ES=1.05	<0.0001
Mental Composite	-0.698 (16.081) 0.426 (-44.799; 33.067) (-4.834; 3.390) n=62 SRM=-0.04 ES=-0.05	0.74	-0.652 (14.725) 0.349 (-35.648; 26.479) (-4.427; 3.087) n=61 SRM=-0.04 ES=-0.05	0.73
For continuous variables Mean (SD) / Median (Min; Max) / (95% CI) / n= / SRM / ES is presented. For comparison within groups 95% CI based on the Fisher´s Non- Parametric Permutation test for matched pairs was used. SRM = Standardized Response Mean= mean difference / SD for difference ES = Effect Size = mean difference / SD for Baseline values Out of 65 patients, four patients lost their prosthesis and should not be imputed at the 2- and 5-year time points. Of those four patients, one patient had SF-36 data (but no Q-TFA data) at 2 years. Thus, the 2-year timepoint includes n=62 at 2 years and n=61 at 5 years.				

Responder analyses for the SF-36 data are presented in **Table 15** using the MCIDs from Keurentjes et al. (2012). These data demonstrate that majority of patients had clinically meaningful improvements on the SF-36, especially with regard to physical function, general health, and vitality. It should be noted that the SF-36 records patients' general health and experiences and is not specific to the implant. Thus, some of the variables below, such as social function and emotional role, should not be considered specific to patients' experience with the OPRA™ Implant System.

Table 15: SF-36 Responder Analyses

Variable	Change from before treatment to 2 years (n=65)	Change from before treatment to 5 years (n=65)
Physical Function improvements		
Success	44 (71.0%)	45 (73.8%)
Not success	18 (29.0%)	16 (26.2%)

Variable	Change from before treatment to 2 years (n=65)	Change from before treatment to 5 years (n=65)
Role Physical improvements		
Success	32 (51.6%)	28 (45.9%)
Not success	30 (48.4%)	33 (54.1%)
Bodily Pain improvements		
Success	34 (54.8%)	32 (52.5%)
Not success	28 (45.2%)	29 (47.5%)
General Health improvements		
Success	44 (71.0%)	47 (77.0%)
Not success	18 (29.0%)	14 (23.0%)
Vitality improvements		
Success	38 (61.3%)	34 (55.7%)
Not success	24 (38.7%)	27 (44.3%)
Social Function improvements		
Success	26 (41.9%)	28 (45.9%)
Not success	36 (58.1%)	33 (54.1%)
Role Emotional improvements		
Success	15 (24.2%)	19 (31.1%)
Not success	47 (75.8%)	42 (68.9%)
Mental Health improvements		
Success	32 (51.6%)	29 (47.5%)
Not success	30 (48.4%)	32 (52.5%)
For categorical variables n (%) is presented. Out of 65 patients, four patients lost their prosthesis and should not be imputed at the 2- and 5-year time points. Of those four patients, one patient had SF-36 data (but no Q-TFA data) at 2 years. Thus, the 2-year timepoint includes n=62 at 2 years and n=61 at 5 years.		

Table 16 presents change in the Q-TFA variables from before treatment to 2 and 5 years for the 65 subjects. As shown, there were statistically significant improvements across all Q-TFA variables (total and individual subscores).

Table 16: Change in Q-TFA Variables from Before Treatment to 2 Years and 5 Years

	Change from before treatment to 2 years (n=65)		Change from before treatment to 5 years (n=65)	
Variable		**p-value within group**		**p-value within group**
Total Q-TFA score	30.1 (16.0) 29.8 (-7.5; 60.8) (26.0; 34.3) n=61 SRM=1.88 ES=1.55	<0.0001	31.8 (16.4) 30.8 (-6.1; 76.8) (27.6; 36.0) n=61 SRM=1.94 ES=1.64	<0.0001
Prosthetic Use score	35.1 (33.4) 29 (-81; 100) (26.6; 43.7) n=61 SRM=1.05 ES=0.98	<0.0001	39.6 (32.7) 29 (-10; 100) (31.2; 48.1) n=61 SRM=1.21 ES=1.11	<0.0001
Prosthetic Mobility score	16.5 (15.6) 17 (-29; 50) (12.6; 20.5) n=61 SRM=1.06 ES=0.80	<0.0001	20.0 (17.4) 20 (-24; 78) (15.5; 24.5) n=61 SRM=1.15 ES=0.97	<0.0001
Problem score	-29.1 (16.1) -31 (-74.3; 7) (-33.3; -25.0) n=61 SRM=-1.80 ES=-1.53	<0.0001	-28.9 (18.2) -32 (-75.3; 17.5) (-33.6; -24.2) n=61 SRM=-1.59 ES=-1.51	<.0001
Global score	39.6 (21.5) 34 (0; 92) (34.1; 45.2) n=61 SRM=1.84 ES=2.04	<0.0001	38.5 (22.7) 33 (-18; 100) (32.7; 44.3) n=61 SRM=1.70 ES=1.98	<0.0001

	Change from before treatment to 2 years (n=65)		Change from before treatment to 5 years (n=65)	
Variable		**p-value within group**		**p-value within group**
For continuous variables Mean (SD) / Median (Min; Max) / (95% CI) / n= / SRM / ES is presented. For comparison within groups 95% CI based on the Fisher´s Non- Parametric Permutation test for matched pairs was used. SRM = Standardized Response Mean= mean difference / SD for difference ES = Effect Size = mean difference / SD for Baseline values Out of 65 patients, four patients lost their prosthesis and should not be imputed at the 2- and 5-year time points. Thus, n=61 for the Q-TFA time points at 2 and 5 years. In the overall success analysis, these four patients are treated as not successes.				

Table 17 presents the responder analyses using the anchor-based MCIDs for the Q-TFA. As shown, majority of patients met the MCID for all Q-TFA variables at 2 and 5 years.

Table 17: Q-TFA Responder Analysis Using Anchor-Based MCID

Variable	Change from before treatment to 2 years (n=65)	Change from before treatment to 5 years (n=65)
Total Q-TFA score MCID improvements		
Success	46 (75.4%)	46 (75.4%)
Not success	15 (24.6%)	15 (24.6%)
Prosthetic Use score MCID improvements		
Success	45 (73.8%)	45 (73.8%)
Not success	16 (26.2%)	16 (26.2%)
Prosthetic Mobility score MCID improvements		
Success	43 (70.5%)	41 (67.2%)
Not success	18 (29.5%)	20 (32.8%)
Problem score MCID improvements		
Success	39 (63.9%)	39 (63.9%)
Not success	22 (36.1%)	22 (36.1%)
Global score MCID improvements		
Success	37 (60.7%)	37 (60.7%)
Not success	24 (39.3%)	24 (39.3%)

Variable	Change from before treatment to 2 years (n=65)	Change from before treatment to 5 years (n=65)
For categorical variables n (%) is presented. Out of 65 patients, four patients lost their prosthesis and should not be imputed at the 2- and 5-year time points. Thus, n=61 for the Q-TFA time points at 2 and 5 years. In the overall success measure, these patients are treated as not successes.		

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. Transfemoral Amputation Osseointegration Study (TFAOS)

As part of PMA approval, the applicant also provided to FDA preliminary data from the ongoing TFAOS study at Walter Reed National Military Medical Center. The current OPRA™ Implant System that is the subject of this PMA is used in this study. There have been no cases of fixture loosening, deep infection, or bent, worn, or fractured abutments in the TFAOS study to date. So far, the changes described above have improved the implant performance.

B. Literature Studies

Several articles have been published based on the same patient population as the OPRA™ study or portions thereof. Key articles are summarized below. Please note that the term osseointegration is used in the literature but is a claim that the applicant will not use for the subject device at this time.

1. Hagberg and Brånemark (2009)

   Hagberg and Brånemark presented 100 patients treated with 106 implants (6 bilaterally; 61% males, 39% females; mean age 43 years; mean time since amputation 11.5 years) between May 1990 and June 2008. Of the 100 patients, 51 are included in the OPRA™ study. The majority had amputations due to trauma (67%) or tumor (21%) (other = 12%). At the time of article publication, 68 patients were using their prostheses (follow-up: 3 months - 17.5 years) and 32 were not (4 are deceased, 7 are before second surgery, 6 are in initial training, 4 are not using prosthesis, and 11 had the implant removed). The majority of treatment failures occurred in patients using pre-OPRA™ systems, before the OPRA™ protocol was established. The implementation of graded rehabilitation is considered to be of utmost importance for improved results.

2. Tranberg et al. (2011)

   Tranberg et al. presented data on the changes in hip and pelvic kinematics in 19 transfemoral amputees, who were treated with an osseointegrated trans-femoral prosthesis. The post-operative gait analysis was carried out at the 2 year follow-up visit. Fifty-seven; age-, side- and gender-matched healthy subjects served as controls. Post-operative data showed that patients who had an osseointegrated transfemoral prosthesis increased their hip

extension by 7.3° (p=0.007), changing from -2.6° (range -13.4° to 10.7°) to -9.9° (range -29.4° to 5°). Moreover, the pre-operative anterior pelvic tilt was reduced by 4.0° (p=0.016), changing from 21.7° (range 11.9-34.8°) to 17.7° (range 5.5-25.7°). Values for hip extension and pelvic tilt changed toward those of controls. These results confirm that patients treated with osseointegrated trans-femoral prosthesis encounter significant changes of their kinematic pattern in terms of hip extension and anterior pelvic tilt. Even though the changes were moderate they may, in the long-term have a positive influence on low-back biomechanics and could contribute to reducing the risk of further problems with low back pain.

3. Nebergall et al. (2012)

The study performed by Nebergall et al. addresses radiostereometric analysis (RSA) and periprosthetic bone remodeling, to assess long-term fixation of the implant system (OPRA™). The following number of implants were analyzed with RSA at each follow-up interval: 47 implants at 6 months, 42 implants at 1 year, 40 implants at 2 years, 15 implants at 5 years, 12 implants at 7 years, and 3 implants at 10 years. The RSA analysis for the OPRA™ system indicated stable fixation of the implant (no substantial motion) up to 7 years after the second surgical procedure. At 5 years, the median (Standard Error) migration of the implant was very small (-0.02 (0.06) mm). The rotational movement was 0.42 (0.32) degrees around the longitudinal axis. There was no statistically significant difference in median rotation or migration at any follow-up time. Although some implants showed slight initial motion, the implants had stabilized at the 5-year follow-up. Of the 3 implants that loosened, the motion detected using RSA was only slightly greater than the median degree of motion in the rest of the cohort. Unfortunately, films for the latest follow-up were only available for the failed implants and films were not taken just prior to implant removal. Kinematics at the latest follow-up did not necessarily indicate loosening or substantial migration. Cancellation of the cortex appeared in at least 1 zone in over half of the patients at 2 years, but the prevalence had decreased by the 5-year follow-up, indicating a stabilization of bone remodeling. The majority of radiographs showed only minimal amounts of bone remodeling around the implant, and ultimately this remodeling did not compromise implant fixation of performance. Even the cases that experienced more moderate bone loss did not show any indication of loosening or implant failure.

Nebergall et al. concluded that there are several distinct advantages in using the OPRA™ system over the use of a conventional socket prosthesis. The transcutaneous nature of the OPRA™ system permits easy attachment and removal of the artificial limb through a quick-release mechanism. Ease of proper attachment also eliminates discomfort from wearing a limb that is improperly fitted. Similarly, since the skin-to-prosthesis interface is minimized and since the dermatological problems often associated with prosthesis attachment occur less frequently; there was only 1 superficial infection per patient every 2 years. Nebergall concluded that he OPRA™ system provides a solution for patients who are unsuitable candidates for a conventional socket prosthesis, due either to amputation that has been at too high a level or due to damage to the stump that has been too severe to allow fitting of a socket prosthesis. The rehabilitation problems identified by Nebergall et al. are consistent with the adverse events summarized above.

4. Brånemark et al. (2014)

The results of the 51-patient OPRA study described in Section X. A-D were published in Brånemark et al. This article is included for completeness. The authors of this peer-reviewed publication concluded that the high cumulative survival rate at two years (92%) combined with enhanced prosthetic use and mobility, fewer

problems and improved quality of life, supported the 'revolutionary change' that patients with transfemoral amputation had reported after treatment with osseointegrated percutaneous prostheses.

5. Tillander et al. (2017)

Tillander, et al. studied the risk of osteomyelitis to characterize the clinical effect of osteomyelitis (including risk of implant extraction and impairments to function), and determine whether common patient factors (age, sex, body weight, diabetes, and implant component replacements) are associated with osteomyelitis in patients using the OPRA™ System.

The study retrospectively analyzed 96 patients that included study subjects within the primary OPRA™ System Study described above. These patients used custom design and commercial OPRA™ System and received femoral implants (102 implants including bilateral treatments; mean implant time, 95 months) treatment between 1990 and 2010 for osteomyelitis. Six patients were lost to follow-up. The reason for amputation was tumor, trauma, or ischemia in 97 limbs and infection in five. All patients were referred from other orthopedic centers owing to difficulty with use or to be fitted with socket prostheses.

Osteomyelitis was diagnosed by medical chart review of clinical signs, tissue culture results, and plain radiographic findings. Proportion of daily prosthetic use when osteomyelitis was diagnosed was semi-quantitatively graded as 1 to 3. Survivorship free from implant associated osteomyelitis and extraction attributable to osteomyelitis respectively was calculated using the Kaplan-Meier estimator. Indication for extraction was infection not responsive to conservative treatment with or without minor debridement or loosening of implant.

Implant-associated osteomyelitis was diagnosed in 16 patients corresponding to a 10-year cumulative risk of 20% (95% CI 0.12–0.33). Ten implants were extracted owing to osteomyelitis, with a 10-year cumulative risk of 9% (95% CI 0.04–0.20). Prosthetic use was temporarily impaired in four of the six patients with infection who did not undergo implant extraction. With the numbers available, an association between age, BMI, or diabetes with osteomyelitis was not identified; however, this study was underpowered on this endpoint.

The authors concluded that although the overall risk of implant osteomyelitis in patients who receive percutaneous osseointegrated implants after transfemoral amputation increases with time, the improved daily living outweighs the risks and inconvenience of treatment for most patients in this respect.

6. Brånemark et al. (2019)

Brånemark, et al. presented 5-year outcomes for a subset of patients in the OPRA™ System Study. Out of 51 patients from the OPRA™ System Study, 40 patients had five-year follow-up data. The five-year fixture cumulative survival rate was 92% and revision-free rate was 45%. The most common AE was superficial infection, occurring 70 times in 34 patients from baseline to the five-year follow-up. Superficial skin infections were normally treated with oral antibiotics for 10 days, but 16 of them required longer treatment. A total of 85 SAEs were reported in 26 patients:

- Removal of the fixture (4 patients)
- Stump revisions (3 patients)

- Deep infections (11 patients)
- Exchange of abutment and/or abutment screw (15 patients)

Fourteen (14) deep infections were diagnosed in 11 patients during the five-year period. One of these infections caused early loosening/failure of the fixture. Nine patients with deep infections were successfully treated with oral antibiotics, with a mean time of five months. One deep infection had not resolved at the five-year follow-up.

Forty-three (43) mechanical complications occurred in 15 patients, resulting in replacement of the damaged abutment and/or the abutment screw. Accidental overload (falling, stumbling causing the abutment to bend) was the cause in sixteen bent abutments in 9 patients. One patient had the abutment temporarily removed (fixture in situ) four months before the five-year follow-up appointment, due to mechanical problems with the abutment and abutment screw.

Analyses of differences between baseline and the five-year follow-up revealed statistically significant improvements in all four Q-TFA scores ($p<0.0001$) and in the physical function (PF) ($p<0.0001$), role physical (RP) ($p=0.020$) and physical component score (PCS) ($p<0.0001$) on the SF-36. All other differences were non-significant. Details of prosthetic use at baseline showed that 29/42 (69%) used their prostheses on a daily basis for at least 13 hours/day. At 5-year follow-up, this was reported by 28/40 (70%) of the patients.

To address a possible relation between higher prosthetic activity and mechanical complications, the group of 40 patients at the five-year follow-up was divided into those that had experienced any mechanical complication to the abutment and/or abutment screw and those without any such complication and compared with regard to their Q-TFA mobility score at the five-year follow-up. The results showed a statistically significant higher mean mobility score in the group of patients that had had a mechanical complication ($p=0.035$). The group with any mechanical complication (n=15) had a mobility score of 74 (SD 20.5, 8-92) as compared to the group without any complication (n=25) which had a mobility score of 64 (SD 20.2, 4-97).

In sum, this study demonstrated that 5-year outcomes were similar to those at 2-year follow-up, and that the benefits were clinically relevant. No additional patients lost the anchorage (fixture) of the implant system. Mechanical complications increased and were more frequent in patients with higher activity. Superficial infections per patient and year remained constant. Though the number of deep infections increased, only one implant had to be removed because of infection. This case was an early deep infection before successful osseointegration had been established.

7. Hagberg et al. (2020)

Hagberg et al. presented long term data with the OPRA™ device, at 2, 5, 7, 10 and 15 years post-S2 surgery. This study includes patients treated in Sweden between January 1999 and December 2017. Thus, original OPRA™ study patients are included, as well as others from the same hospital outside the original OPRA™ study. Integrum is not the sponsor of this study. In addition, several versions of the OPRA™ device are included in this study, and it should be noted that some patients were treated off-label in Sweden. Despite these limitations, the Q-TFA scores generally demonstrated significantly more prosthetic use, better mobility, fewer problems, and an improved global score at 2, 5, 7, and 10 years compared with baseline. At 15 years, there is

limited patient data but what data are available (see Figure 4 in Hagberg, et al. (2020); n=11 for prosthetic use subscore and n=9 for other subcores) show maintenance in the prosthetic use and mobility subscores and improvement in the problem and global Q-TFA subscores from 2-year data.

XII. PANEL MEETING RECOMMENDATION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedics and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Clinical experience with the OPRA™ Implant System indicates that patients implanted with the OPRA™ Implant System experienced statistically significant and clinically meaningful improvements in prosthetic use, mobility, level of function, and quality of life after two and five years. The number of subjects using their prosthetic device increased during the study, both on an hourly and daily basis, demonstrating patient satisfaction with using the prostheses.

Outcomes from the 2-year OPRA™ study are supported by an additional analysis and endpoints that measure device safety and effectiveness with 65 subjects (51 subjects from the original OPRA™ study and 14 additional subjects) at 2 and 5 years. Majority of patients (70.8% of 65) met the new primary effectiveness endpoints (i.e., total Q-TFA score achieved MCID and met radiographic success) and second effectiveness endpoints (each Q-TFA subscore achieved MCID) defined for the 65-patient cohort at 2 and 5 years. Changes over time in the SF-36 and Q-TFA scores further support device effectiveness.

The provided clinical data supports the effectiveness of the OPRA™ Implant System for patients who have transfemoral amputation due to trauma or cancer and who have or are anticipated to have rehabilitation problems with, or cannot use, conventional socket prosthesis.

B. Safety Conclusions

Infection, mechanical complications, and pain were the most frequent reported AEs in the OPRA™ study, as expected for an osseointegrated device. As noted, in the original 51-patient OPRA™ study, after 2 years, there were 28 subjects with 40 superficial infections, 3 subjects with 4 deep infections and 4 subjects with 9 events of mechanical complications. After 5 years, 34 subjects had 70 superficial infections, 11 subjects had deep infections, and 15 subjects had 43 mechanical complications. In the 65-patient cohort, using the new safety endpoint in the 65-patient cohort, 67.7% of patients met this endpoint at 2 years and 43.1% at 5 years. Cumulative survival rate of the Fixture was 93.6% and 94% in terms of patient survival and implant survival, respectively, at both 2 and 5 years, with an assumption that non-observed data is non-informative at 5 years.

Superficial skin infections were normally treated with oral antibiotics, most deep infections (i.e., defined as extending below fascia) were successfully treated with oral antibiotics, and mechanical complications resulted in

replacement of the damaged abutment and/or the abutment screw. As noted, preliminary data from the ongoing TFAOS study so far support that the company's incremental improvements to the device address the infection and mechanical complications previously observed with the OPRA™ Implant System.

The risks associated with this device should be compared to the amputated population as a whole. For instance, up to 72% socket-related problems including pain, skin sores and discomfort from socket suspended prosthesis were reported during a four-week period by a group of 97 transfemoral non-vascular amputees who were mailed the Q-TFA [Hagberg and Brånemark (2001)]. In the original 51-patient OPRA™ study, the incidence of pain and discomfort is less than 15% over a period of 2 years, and superficial infections have an incidence of 55% during a 2-year period. Superficial infections per patient and year remained constant between 3 and 5 years. The incidence of revision requiring removal of the entire OPRA™ Implant System was 8% at 2 years.

The underlying cause of amputation contributes to the risk of reoperation and complication. In trauma patients, the prevailing demographic is young male patients. One study of major limb amputations at a level 1 civilian trauma center showed 0.14% (74/52,000) of patient admissions sustained traumatic lower extremity amputation [Kobayashi *et al.* (2011)]. Of these, 17 (23%) were transfemoral amputations. The complication rate was 32.4% overall. Extremity related complications included osteomyelitis, compartment syndrome, and cellulitis while non-extremity related complications include renal failure, pulmonary insufficiency and pneumonia. Furthermore, military trauma patients are more likely to sustain higher energy injuries. Associated complications include heterotopic ossification, compartment syndrome, infection, neuroma and myodesis failure. They have a high reoperation rate at 53% overall [Tintle *et al.* (2014)]. Indications for reoperation in the transfemoral trauma patients include heterotopic ossification excision (41%), wound infection (20%), scar revision (11%), myodesis failure revision (10%), neuroma excision (5%), and wound dehiscence (4%).

While the trauma population tend to be younger and healthier, the vasculopathic population tends to be older with more comorbidities. In a 10-year population based cohort study of 170,000 patients with peripheral vascular disease, 290 received an initial lower extremity amputation with 32 of these at the transfemoral level [Johannesson *et al.* (2009)]. Of the 290 lower extremity amputees, 43 underwent contralateral amputation and 53 underwent reoperation for revision amputation during that same time period.

Thus, risks with the OPRA™ Implant System are consistent with those experienced by the transfemoral amputee population generally, while improving daily living and providing other benefits to patients. In sum, the safety results are reasonable for this amputee population who have limited other options. The alternative for patients who have problems with sockets is minimal or no ambulation, or even permanent confinement to use of a wheelchair which greatly inhibits their daily life and ability to lead independent lives. Use of the OPRA™ Implant System presents risks to patients, but these risks are consistent with those for amputees generally, and the socket related risks are even more pronounced in the intended use population. Specifically, all amputees have risks for infections and re-operations. Study data with the subject OPRA™ Implant System demonstrate that these risks are manageable, can be mitigated, and further, that the benefits with OPRA™ Implant System outweigh the risks.

This data supports the safety of the OPRA™ Implant System for the proposed indications.

The rate of overall success (i.e., success in both the primary effectiveness and safety endpoints) were 47.7% and 35.4% at 2 and 5 years, which indicates that at 2 years, 90.8% of patients had some level of success, whether effectiveness, safety, or both. The same is true for 78.5% of patients at 5 years.

C. Benefit-Risk Determination

Transfemoral amputation constitutes a severe handicap and reduces quality of life. Reported problems with socket prostheses include socket related pain, recurrent skin infections and ulceration in the socket contact area, a short stump, volume fluctuation of the stump, soft tissue scarring, extensive areas of skin grafting, socket retention problems due to excessive perspiration, or discomfort limiting everyday activities.

Osseoanchored prostheses were developed as an alternative to conventional socket prostheses and are intended to offer transfemoral amputation patients several benefits and advantages. The OPRA™ study has shown the following benefits:

- Improved range of movement around the hip joint, as motion was unimpeded by a socket brim. This was demonstrated by increased range of motion scores from baseline to 24 months;
- Increased prosthetic use, level of function and mobility, including longer walking distances and increased sitting comfort as demonstrated by improvements in Q-TFA sub scores to 5 years;
- Improved quality of life as demonstrated by the Q-TFA to 5 years;
- Eliminated socket related soft tissue problems to 5 years;
- Reduced physiological cost;
- Increased abduction/adduction testing, and improvement in walkability to 5 years;
- Improved lower extremity proprioception.

During the 2 year 51-patient prospective clinical study, the following risks were the most frequently identified as associated with the prostheses:

- Superficial infection: 28 (55%) subjects with 40 events
- Deep infection: 3 (6%) subjects with 4 events
- Mechanical complication of the implant: 4 (8%) subjects with 9 events
- Pain: 6 (12%) subjects with 6 events
- Injury: 4 (8%) subjects with 4 events

Similar events were observed in these patients at 5 years and the additional 14 patients at 2 and 5 years, and in the commercial data collected since HDE approval. As noted in the Summary of Safety and Probable Benefit for the HDE device, FDA concluded that the probable benefits outweighed the risks associated with the OPRA™ Implant System as the physical and prosthetic advantages led to improvement in candidates' comfort, function and quality of life. Frequent adverse events experienced by users of the OPRA™ Implant System have generally been temporary in nature. Notably, in two out of four cases of implant failure in the 51 subject pivotal study used for the HDE approval, the subjects elected to have the OPRA™ device re-implanted. Risks of the OPRA™ Implant System can be effectively managed by individualized prosthetic components, as well as appropriate physical rehabilitation, activity and health management.

Additional factors to be considered in determining probable risks and benefits for the OPRA™ Implant System device included:

1. Patient Perspective

Patient perspectives considered during the review included:

The applicant also provided patient perspective data from OPRA™ Implant System patients after at least 5 years post stage 2 surgery. Specifically, patients from the original OPRA™ study were asked if the advantages outweigh the disadvantages of using the OPRA™ device when taking into account surgeries, rehabilitation and possible adverse events (e.g., abutment changes, superficial infections). Responses were received 5 years and an average 8.5 years after stage 2 surgery. Responses were recorded using a 5-point scale of "no, highly" to "yes, highly." The vast majority of responses at both time points were that patients "highly" thought the advantages outweighed the disadvantages of the OPRA™ Implant System.

The OPRA™ Implant System is considered a rehabilitation alternative when treatment with socket prostheses is unsatisfactory or anticipated to be significantly problematic. As noted, the OPRA™ Implant System was able to provide patients in the OPRA™ study with numerous benefits to improve their mobility and physical function, increase prosthetic use, and improve quality of life. Similar outcomes have been reported long term for patients in the same study, other clinical experience, and for patients using the device after HDE approval. The numerous benefits from the OPRA™ Implant System are weighed against known risks associated with osseointegrated implants. The clinical data and analyses provided in this PMA further support that the probable benefits outweigh the probable risks for the OPRA™ Implant System.

D. Overall Conclusions

The nonclinical and clinical data presented in this application support the reasonable assurance of safety and effectiveness of this device, which has had HDE approval since 2015, when used in accordance with the indications for use. Specifically, effectiveness of the OPRA™ Implant System was demonstrated by evaluating the Q-TFA, a self-reported measure developed for nonelderly transfemoral amputees using a socket or osseointegrated prosthesis which evaluates prosthetic use, mobility, problems, and global health under separate subscores and radiographic data. Subjects experienced statistically significant and clinically meaningful improvements in prosthetic use, prosthetic mobility and decreased problems. Safety of the OPRA™ Implant System was demonstrated by evaluating subsequent secondary surgical interventions and superficial infection occurrences. Cumulative survival rate of the implant fixture was as high as 93.6% and 94% in terms of patient survival and implant survival, respectively, at both 2 and 5 years. Adverse events including infection, mechanical complications, and pain are as expected for an osseointegrated device, which can be effectively managed by individualized prosthetic components, as well as appropriate physical rehabilitation, activity and health management. These data are supported by long-term follow-up and other studies where similar effectiveness and safety profiles were demonstrated.

XIV. CDRH DECISION

CDRH issued an approval order on December 18, 2020. The final clinical conditions of approval cited in the approval order are described below.

As a condition of approval, the applicant agreed to conduct the two Post-Approval Studies (PAS) as described below:

1. **Transfemoral Amputation Osseointegration Study (TFAOS) PAS** is a prospective, multicenter, cohort study to provide an ongoing assessment of the short-term (2 years) safety and effectiveness of the updated version of the OPRA™ Implant System (e.g., improvements with components, Axor™ II, and instrumentation since the H080004 pivotal study). A total of 50 consented transfemoral amputee patients, aged 22 to 65 years, will be enrolled consecutively at two sites in the United States. The Questionnaire for Persons with Transfemoral Amputation (Q-TFA) assessment will be administered at baseline and at 3, 6, 12 and 24 months after stage-2 surgery. Radiological assessments of osseointegration will be measured pre-operatively and post-operatively following stage-2 surgery.

   The **primary endpoints** are as follows: (1) The rate of overall success at two years. The overall success is the composite primary safety and effectiveness endpoint. The primary safety endpoint is defined as no subsequent secondary surgical interventions, and, at most, 2 superficial infections at two years. The primary effectiveness endpoint is the achievement of the minimal clinically important difference (MCID) for the total Q-TFA score (mean of all subscores, i.e., prosthetic use score, prosthetic mobility score, problem score, and global score) of 20.25 points, and radiographic success, defined as no radiographic loosening of the implant with a radiolucent zone wider than the thread depth surrounding the entire implant. (2) Proportion of patients who achieved either/or/none of primary safety endpoint or primary effectiveness endpoint at 2 years. The **secondary endpoint** is the proportion of patients who achieved the MCID for the Q-TFA Prosthetic Use sub score (19 points), Prosthetic Mobility sub score (11 points), Problem sub score (-23 points) and Global sub score (33 points), individually at 2 years after stage-2 surgery.

2. **Osseointegration Quality Registry PAS** is a registry conducted by Walter Reed National Military Medical Center to provide ongoing assessment of the short term (2 years) safety and effectiveness of the updated version of the OPRA™ Implant System (e.g., improvements with components, Axor™ II, and instrumentation since the H080004 pivotal study), and the long-term (5 years) safety and effectiveness of the OPRA™ Implant System. The registry will consecutively enroll up to 50 subjects from the TFAOS PAS and additional consented transfemoral amputees, aged 18 to 67 years, for a total of 100 subjects at multiple sites in the United States. The Questionnaire for Persons with Transfemoral Amputation (Q-TFA) will be administered at baseline, following stage-2 surgery, and every 6 months through a 5-year follow-up after stage-2 surgery. Radiological assessments of osseointegration will be measured pre-operatively and post-operatively following stage-2 surgery.

   The **primary endpoints** are as follows: (1) the rate of overall success at 2 and 5 years. The overall success is the composite primary safety and effectiveness endpoint. The primary safety endpoint is defined as no subsequent secondary surgical interventions and at most 2 superficial infections at 2 years; no subsequent secondary surgical interventions and at most 3 superficial infections at 5 years. The primary effectiveness endpoint is the achievement of the minimal clinically important difference (MCID) for the total Q-TFA score (mean of all subscores, i.e., prosthetic use score, prosthetic mobility score, problem score, and global score) of 20.25 points; and radiographic success, defined as no radiographic loosening of the implant with a radiolucent zone wider than the thread depth surrounding the entire implant. (2) Proportion of patients who achieved either/or/none of primary safety endpoint or primary effectiveness endpoint at 2 and 5 years. The **secondary endpoint** is the proportion of patients who achieved the MCID for the Q-TFA Prosthetic Use sub score (19 points), Prosthetic Mobility sub score (11 points), Problem sub score (-23 points) and Global sub score (33 points), individually at 2- and 5-years following stage 2 surgery.

The applicant's manufacturing facilities have been determined, through prior on-site inspection and (due to constraints posed by the COVID-19 pandemic) by a review of relevant manufacturing site documentation and compliance history, to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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