SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name:	Osseoanchored Prostheses for the Rehabilitation of Amputees
Device Trade Name:	OPRA
Applicant Name:	Integrum AB
Applicant Address:	Krokslätts Fabriker 50 SE-431 37 Mölndal SWEDEN

Date(s) of Panel Recommendation:	None
Humanitarian Device Exemption (HDE) Number:	H080004
Humanitarian Use Device (HUD) Designation Number:	08-0197
Date of Good Manufacturing Practices Inspection:	May 21, 2015
Date of Humanitarian Use Device (HUD) Designation:	July 11, 2008
Date of Notice of Approval to Applicant:	July 16, 2015

II. INDICATIONS FOR USE

- The OPRA device is indicated for patients who have transfemoral amputation due to trauma or cancer and who have rehabilitation problems with, or cannot use, a conventional socket prosthesis. The OPRA device is intended for skeletally mature patients.
- The patient failed to receive benefit from a socket prostheses 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 contraindications for the OPRA device follow.

1. The patient's skeletal growth is not complete. Completed skeletal growth is defined through the finding of generally closed epiphyseal zones on X-ray.
2. The patient has atypical skeletal anatomy which may affect treatment with OPRA. 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.
3. The patient would have less than 2 mm of remaining cortex bone available around the implant, if implanted.
4. The patient has osteoporosis.
5. The patient is older than 65 years or younger than 22 years.
6. The patient's body weight is higher than 220 lbs including the prosthesis.
7. 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.
8. The patient is pregnant.
9. The patient is not expected to be able to comply with treatment and follow up requirements.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the OPRA device labeling.

V. DEVICE DESCRIPTION

The implant components are described below, divided into the two surgical stages and external prosthetic components.

Implant components for the Stage 1 surgery (Figure 1):

- Fixture
- Central Screw
- Healing Cylinder
- Cylinder Screw
- Graft Screw

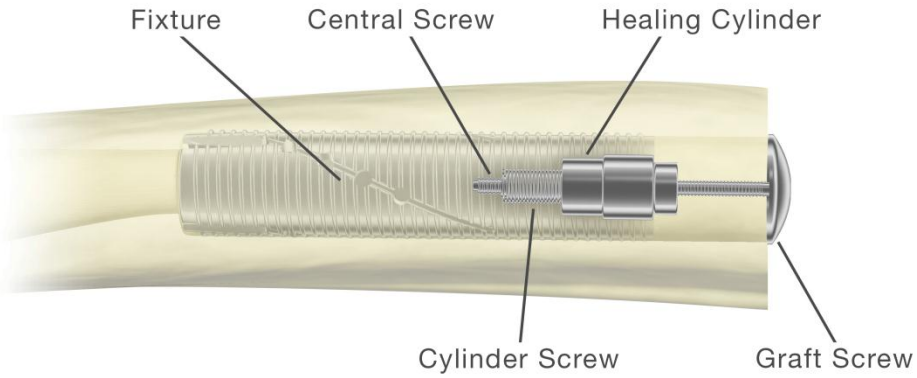

Figure 1. Components - S1: Fixture, Central Screw, Healing Cylinder, Cylinder Screw and Graft Screw inserted in the bone.

Implant components for the Stage 2 surgery (Figure 2):

- Abutment
- Abutment Screw

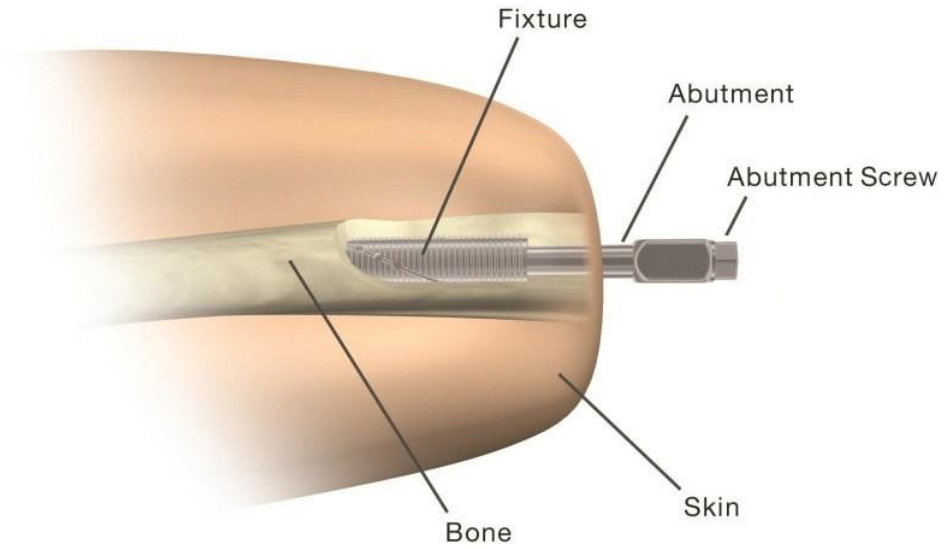

Figure 2. Components - S2: Abutment and Abutment Screw inserted in the Fixture (superior cortex removed for visualization of the device).

External prosthetic components:

The implant components should be connected to external prosthetic components through the connection device OPRA Rotasafe. For detailed information, see the OPRA Rotasafe Manual.

The OPRA Implant System is approved for use only with the prosthetic components manufactured by Otto Bock, specified in the Prosthetic Protocol, Section 8. Use of prosthetics other than the components specified is considered off-label use of the device.

List of Components:

Table 1. List of components

Component		Ref.no.
Central Screw		IBC0001
Healing Cylinder		IBC0002
Cylinder Screw		IBC0017
Graft Screw		IBC0018
Fixture	**Diameter (mm)**	
Fixture	Ø 16	IBC0008
Fixture	Ø 16.5	IBC0009
Fixture	Ø 17	IBC0010
Fixture	Ø 17.5	IBC0011
Fixture	Ø 18	IBC0012
Fixture	Ø 18.5	IBC0013
Fixture	Ø 19	IBC0014
Fixture	Ø 19.5	IBC0015
Fixture	Ø 20	IBC0016

Component		Ref.no.
Abutment	**Length (mm)**	
Abutment	72	IBC0026
Abutment	72+1*	IBC0050
Abutment	72+2**	IBC0051
Abutment	77	IBC0027
Abutment	77+1*	IBC0057
Abutment	77+2**	IBC0058
Abutment Screw		
Abutment Screw	82	IBC0033
Abutment Screw	87	IBC0034
OPRA Rotasafe		IBK0018

** Pressfit diameter increased by 0.01 mm*
*** Pressfit diameter increased by 0.02 mm.*

The Fixture, Abutment, Central Screw, Healing Cylinder, Cylinder Screw and Graft Screw are manufactured from commercially pure titanium (Ti), and the Abutment Screw is comprised of wrought titanium 6-aluminum 4-vanadium alloy. The materials conform to ASTM-B348-97 "Standard specifications for Titanium and Titanium Alloy bars and billets."

Figure 3 shows the OPRA device as used with an amputation prosthesis attached.

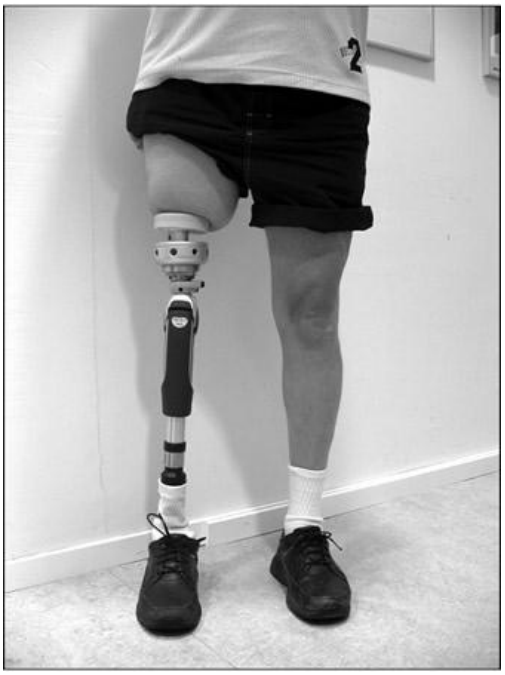

Figure 3: The OPRA Device with Amputation Prosthesis Attached

The primary components of the OPRA device are the Fixture and the Abutment. The Fixture is threaded and designed for anchoring in the medullary canal of the remaining femur. The Abutment provides a skin-penetrating connection between the Fixture and the prosthesis.

The OPRA device is implanted in a two-stage surgical procedure. In Stage I, the distal part of the femur is exposed, preferably using a ventral approach, which will leave a long dorsal flap. By the use of fluoroscopy and guiding devices, the correct position of the Fixture in the medullary canal is found. The canal is reamed step by step to a proper diameter for insertion of the implant. The Fixture is installed intramedullary. A myodesis is performed. A Central Screw, Healing Cylinder, Cylinder Screw and Graft Screw are inserted, and the wound is closed. The sutures are removed approximately 3 weeks post-operatively. The Fixture should remain unloaded for six months to allow for it to become anchored in the femur.

In the Stage II surgery, which occurs approximately 6 months after the first surgery, the femur is exposed via the incision from the Stage I-Surgery. The

Healing Cylinder, Cylinder Screw and Graft Screw are removed and the tissues are trimmed. The Abutment is inserted to the Fixture transcutaneously and secured by the Abutment Screw (bolt). The skin in the Abutment area is trimmed to almost split-skin thickness and attached to the distal end of the bone to prevent skin movement. Sutures are removed approximately 3 weeks postoperatively.

After skin healing the patient begins rehabilitation. The Fixture is gradually loaded by training with a short temporary prosthesis. All early training is performed under supervision of a trained Physical Therapist. Full weight bearing will not be allowed until approximately six months after Stage II-Surgery. Once training is completed, the prosthesis is attached and the patient can ambulate. The prosthetist will help with proper fitting of the prosthesis.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The rehabilitation of transfemoral amputees has traditionally been performed using socket prostheses; however, the indication for use for the OPRA device is for patients who have rehabilitation problems with, or cannot use, a conventional socket prosthesis. For example, in some patients, the use of a socket prosthesis 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 device has been CE marked for 15 years and 224 devices have been sold in Europe since 2000. In addition, devices have been sold in Australia (n=20), Chile (n=20), and Jordan (n=2). The OPRA device has not been withdrawn from any market for reasons relating to the safety and effectiveness of the device.

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.

Table 2: Potential adverse effects on health

Potential adverse effects
Superficial Infection
Mechanical complication of Abutment or Abutment Screw
Pain
Loosening of the Fixture
Deep Infection
Injury
Bone Fracture
Skin necrosis
Pyrexia
Soft tissue necrosis
Chills
Impaired healing
Wound necrosis
Joint injury
Post procedural haematoma
Myositis
Blister

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Biocompatibility Studies

The OPRA device is manufactured from Titanium materials (Ti-6Al-4V and commercially pure titanium) conforming to ASTM B348-97. The materials used for the OPRA device have been used for implantable devices for many years. Therefore, biocompatibility testing is not required as the materials are known to be acceptable implantable materials.

B. Mechanical Testing

As summarized below, the objectives of the torsion and bending testing were to ensure that the device is capable of withstanding expected *in vivo* loading. The objective of the wear and fatigue testing was to evaluate the effect of torsional moments of the estimated clinical worst case of 15 Nm acting on the OPRA Implant System and the resulting potential for wear and fretting. As the Rotasafe component is intended to protect the implant system from unfavorable rotational mechanical loads, axial, bending and torsion testing were performed to ensure that the device performed as expected.

Torsion Testing

Torsion fatigue testing was conducted by rigidly clamping one end of the test piece and applying a moment to the other end. The testing was performed using a sine wave loading pattern at 10 Hz, with the critical implant interfaces tested in air and tested in aerated saline solution at 37°C. Three tests were performed with the implant exposed to air, and these three implants survived 10 million cycles. However, when tested with the bearing surfaces in 37°C aerated saline solution, the implants did not pass the cyclic torsion test at 17 Nm. There was excessive wear debris and a notable change in the Fixture's internal geometry. Excessive wear was observed in the Fixture and on the Abutment. As the device survived 10 million cycles at a higher load without saline, it can be determined that the saline environment adversely affected the results of the cyclic torsion test. It is important to note that the connection between the Fixture and Abutment is not exposed to saline solution in the patient. Therefore, it can be concluded that the device should perform as intended as the device withstood 10 million cycles of torsional loading at 35 Nm.

Bending Testing

Four point bend fatigue testing was conducted with a "worst-case" scenario for implant fixation, representing severe bone loss around the implant and using the smallest diameter Fixture (16 mm Fixture). The bending fatigue test was performed using a sine wave loading pattern at 10 Hz, with the critical implant interfaces soaked in aerated saline solution at

37°C. Four OPRA devices were tested in bending at 50 Nm. All 4 devices survived 10 million loading cycles without any visible cracks (examined with 4X magnification).

Based upon the above testing, the OPRA device should be able to withstand the loads encountered during the average daily activities of a 100-kg patient. Specifically, these mechanical requirements were determined to be minimum 1000N vertical force, minimum 75 Nm $M_{sagittal/frontal}$, and 20 Nm M_{torque}.

Wear and Fatigue Testing

The purpose of the test was to evaluate the effect of torsional moments of the estimated clinical worst case of 15 Nm acting on the OPRA Implant System and the resulting potential for wear and fretting. The evaluation tested 3 constructs of OPRA Implant System, each construct consisting of the components as listed below:

- Abutment,
- Abutment Screw, and
- Fixture.

The components tested are considered worst case as the geometries engaged in the rotational load are identical for all configurations. The Abutment Screw was tightened to 12 Nm. The constructs were tested in parallel at a maximum torque of 15 Nm in both directions for up to 5 million cycles at a maximum frequency of 2 Hz. All tests were performed in bovine serum diluted to 20g/l protein content and maintained at 37°±1°C. Subsequent to the wear simulator testing, the tested devices were evaluated by SEM and the overall titanium wear debris for the full test run was determined. All samples survived 5 million cycles of worst case 15 Nm loading without failure. In addition, visual analyses confirmed that there were no fractures or microcracks of the implant components.

SEM photographs showed wear debris in two areas:

- the press-fit area of the cylindrical portion of the Abutment approximately 10mm above the hex, and

- the hex of the Abutment.

The wear in the press-fit area showed both abrasive and adhesive (fretting) wear. The fretting wear is typical of the order of <20µm wide/deep and does not show the sharp geometries that would have acted as efficient stress concentrators. The hex-area shows only insignificant wear. In addition, some of the wear seen may attributed to the polishing process conducted during device production. No micro cracks were seen in either sample analyzed. The consistent angular displacement throughout the 5 million cycles of the test confirmed that the OPRA device is a stable mechanical joint.

The worst case wear rate is estimated to be 0.04 mm^3/year (1 M steps). These results can be compared to those reported in literature for wear seen in total hip replacements (THR), which are 10-200mm^3/year for metal on polyethylene total hip systems and 0.3-5 mm^3/year for metal on metal total hip systems. Therefore, the wear of the OPRA system is less than what is reported for total hip systems by an order of magnitude of 250-5000 times as compared to metal on polyethylene total hip systems and 7-125 times as compared to metal on metal total hip systems. Therefore, the potential for wear is a low risk for the OPRA system.

Wear and fatigue testing demonstrated that the OPRA device is able to withstand the expected load of average daily activities for a transfemoral amputee, while maintaining a stable mechanical joint and minimizing the potential for fretting, fretting corrosion, and wear. Based on the results of this testing, the OPRA device is capable of withstanding expected loading and should perform as intended.

<u>Rotasafe Mechanical Testing</u>

The Rotasafe was subjected to the following testing:

- Axial Testing (twice the maximum body weight): The abutment jig was placed in the abutment clamp of the Rotasafe. Three axial loads of over 2000N were applied axially via the abutment jig. At 100kg, a 0.2 mm compression was seen in the system.

- Bend testing (twice the expected bending moment): A bending test jig was attached to the prosthesis attachment plate and was clamped to the test machine. The abutment jig was placed in the abutment clamp of the Rotasafe and over 100Nm force was applied. At 50 Nm there was a 0.13" movement in the system.

- Torque testing (moments until the device releases into protection mode): An abutment jig was placed in the abutment clamp of the Rotasafe and was clamped to the device in the test machine. A torsion test jig was attached to the prosthesis attachment plate and was loaded to apply a torsion moment. Sixteen torque tests were performed with 4 or 6 press screws at different settings. The release levels for 4 press screws were between 10 – 15Nm. Each release level setting was tested 3 times. In addition, 22 torque tests were performed on a Rotasafe that had been used by a patient for one week. The tests showed the release moments after many releases was approximately double the pre-patient trial release levels. The problem was located to the surfaces and fit between the plunger and housing of the press screw. Damage occurred after 50 overload cycles.

The results showed that the Rotasafe performs as expected during axial and bending tests. Initial torque tests were successful; however, many releases caused damage to the press screws resulting in an increase in the release level. As a result, maintenance after 5 overloads is emphasized in the patient information and User Manual.

C. Sterilization

All implant components are sterilized with gamma sterilization.

D. Shelf Life Information

The OPRA Implant System has a 5 year shelf life.

X. SUMMARY OF CLINICAL STUDIES

Introduction

Since 1990, patients with amputations having osseoanchored devices implanted have been followed clinically in order to assess the safety and effectiveness of the devices, for the benefit of the patients as well as optimization and standardization of the surgical and rehabilitative procedures.

Summary of the OPRA Implant Clinical Investigation

Study Design

A prospective investigation was performed at Sahlgrenska University Hospital, Gothenburg, Sweden 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 subjects were bilateral subjects. Forty-five patients were unilateral subjects. Due to the small sample size of the bilateral patients, this group was unable to separated and studied alone. The length of the study was 2 years.

Criteria for inclusion into this prospective study were:

- Transfemoral amputee patients with problems using a conventional socket prosthesis
- Undergone pre-operative Radiographic assessment including CT of the femur stump
- Skeletal maturity
- Normal anatomy
- Body weight less than 100 kg (225 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

A subject was excluded if:

- 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

The following table is the accountability table of the subjects in the study.

Table 3: Accountability Table

	Baseline	12 months	24 months
Theoretical	51	51	51
Deaths (cumulative)	0	1	1
Missing (cumulative)	0	1	1
Removed from Study (cumulative)	0	1	4
Expected	51	49	46
Actual[A]	47	42	36
Actual[B]	51	47	45
% Follow-up ITT	100.0%	95.9%	97.8%

Theoretical – [Deaths +Revisions/Removals] = Expected

% Follow-up = Actual[B] / Expected X 100, expressed as a percentage.

[A]Subjects with complete data for each endpoint, evaluated per protocol, in the window of time, defined in 13.2.2.4.

[B]Subjects with any follow-up data reviewed or evaluated by the investigator ("all evaluated" accounting).

As noted in Table 3 above, six subjects discontinued the study. Five of these subjects had AEs at the time they discontinued the study; 3 subjects experienced loosening of the OPRA Implant System and were considered device related failures, 1 subject committed suicide and 1 subject that was lost to follow-up. The sixth subject got a knee injury in the contralateral knee. This made it impossible for the subject to adhere to the rehabilitation program.

One additional subject was revised soon after the 24 month window. This patient is considered a failure throughout the rest of study description. The study has a total of 4 revision cases.

The following table is the demographics of the subjects.

Table 4: Demographics

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
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 been using prosthesis if not Prosthetic user at inclusion	8 (88.9%)
Social description	
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

The general study objectives were:

- To evaluate the performance of OPRA Implant System when used for the intended purpose, under normal conditions and according to instructions.
- To evaluate complications with OPRA Implant System when used for the intended purpose, under normal conditions and according to instructions.

The primary objective of the clinical investigation was to evaluate the improvement of Prosthetic Use Score captured by the Questionnaire for persons with a Transfemoral Amputation (Q-TFA) questionnaire, comparing the OPRA Implant System to Baseline (i.e. to socket prosthesis).

The secondary objectives were:

- To evaluate improvements in functional ability when using the OPRA Implant System.
- To evaluate improvements in quality of life when using the OPRA Implant System.
- To evaluate the frequency of possible medical complications when using the OPRA Implant System.
- To evaluate the type and frequency of mechanical complications when using the OPRA Implant System.

Probable Benefit

The main efficacy measure was the Q-TFA. The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a new self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100).[7] The use of the OPRA Implant System was able to provide subjects with benefit as measured by increase in prosthetic use (both number of days and hours per day), level of function, and quality of life. The number of subjects stratified by hours per day of prosthesis use are reported at baseline, 12 months and 24 months in Figure 4. Figure 4 shows that the number of subjects using their prosthetic more than 12 hours a day increased.

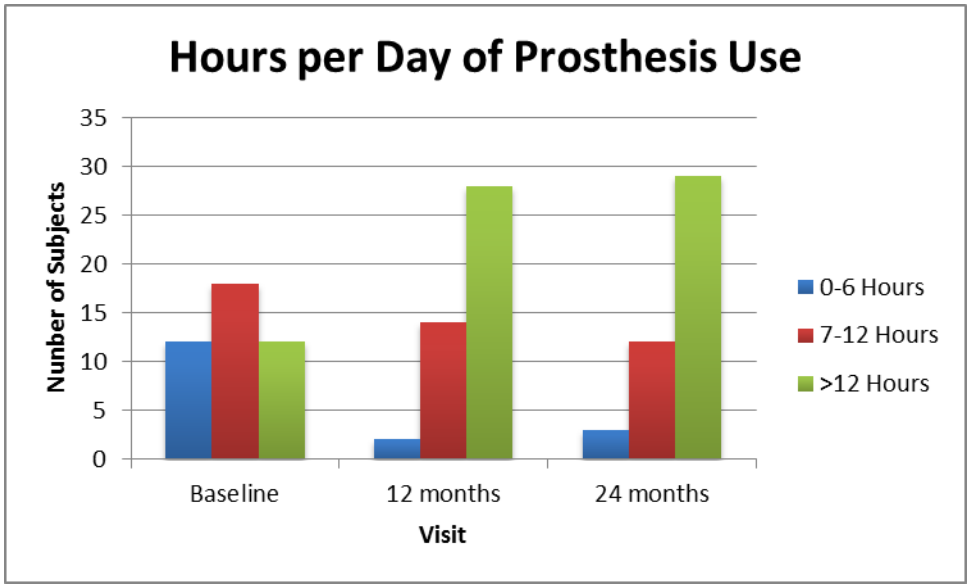

Figure 4: Hours per Day of Prosthesis Use by Visit

The number of subjects stratified by days per week of prosthesis use are reported at baseline, 12 months and 24 months in Figure 5.

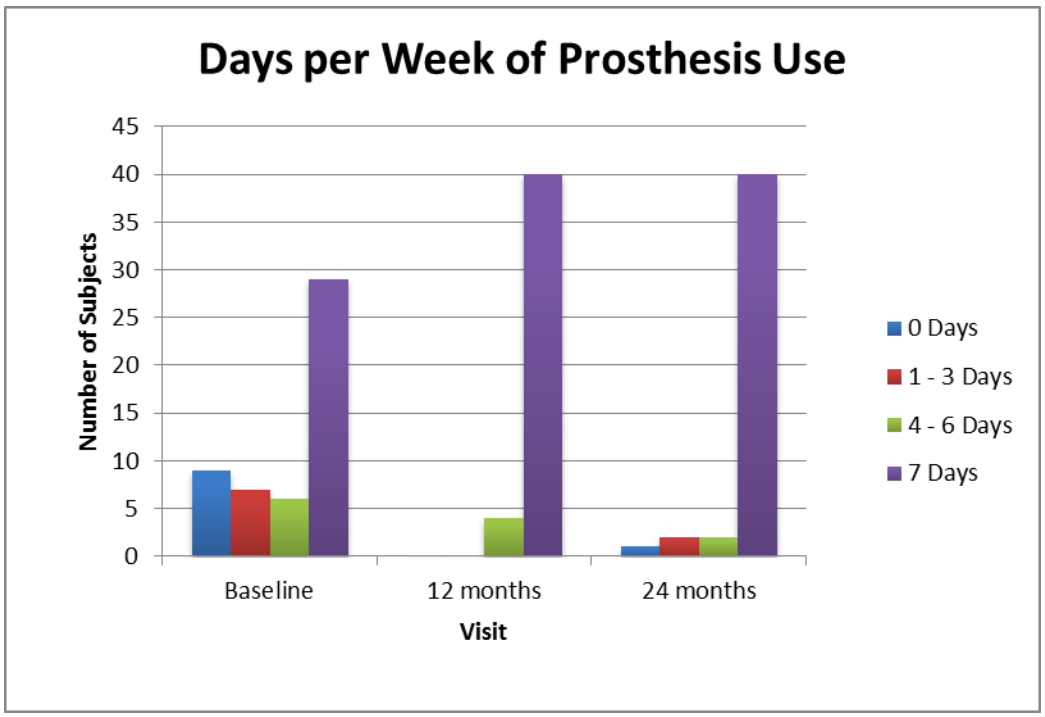

Figure 5: Days of Prosthesis Use per Week by Visit

Figure 5 shows the increase of prosthetic use from baseline to 2 years. The prosthetic use score, level of function, mobility, and improvement in quality of life significantly increased from baseline to 12 and 24 months, while the problem score significantly decreased during the same periods.

As the primary endpoint, the mean Prosthetic use score at baseline was 46.7 (Standard Deviation 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). 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. Implant cumulative survival rate after two years of follow up is 92% and 93% on patient or implant level, respectively.

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 6. Figure 6 shows that low prosthetic users (<25) saw a large increase in prosthetic use at 2 years. The moderate prothetic users saw a slight increase and the high functional prosthetic users saw a slight decrease.

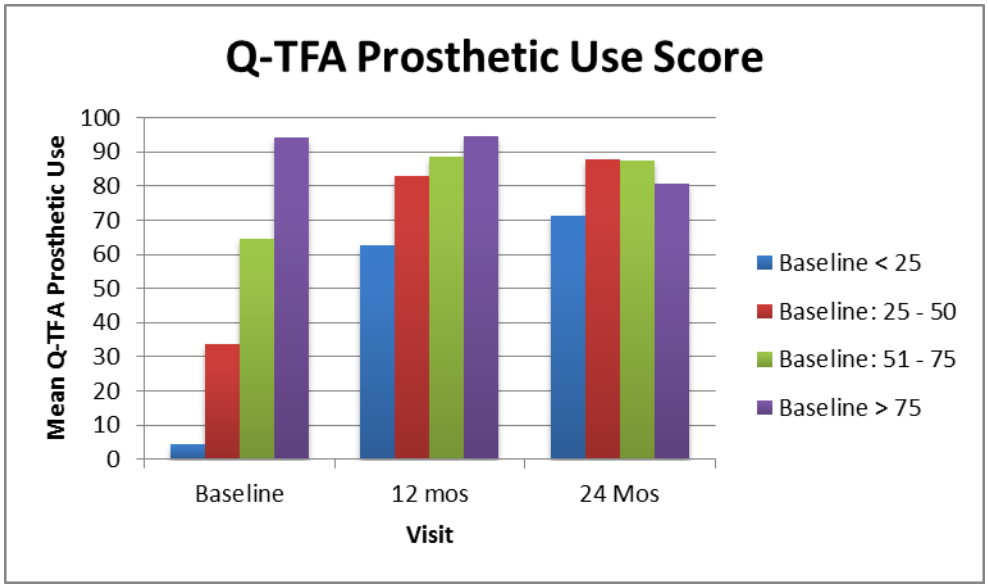

Figure 6: Mean Q-TFA Prosthetic Use Score by Visit

The average of the Q-TFA Problem Score stratified by baseline score and the changes in scores at 12 and 24 months post-procedure are shown in Figure 7. All groups showed a decrease in the problem score at two years.

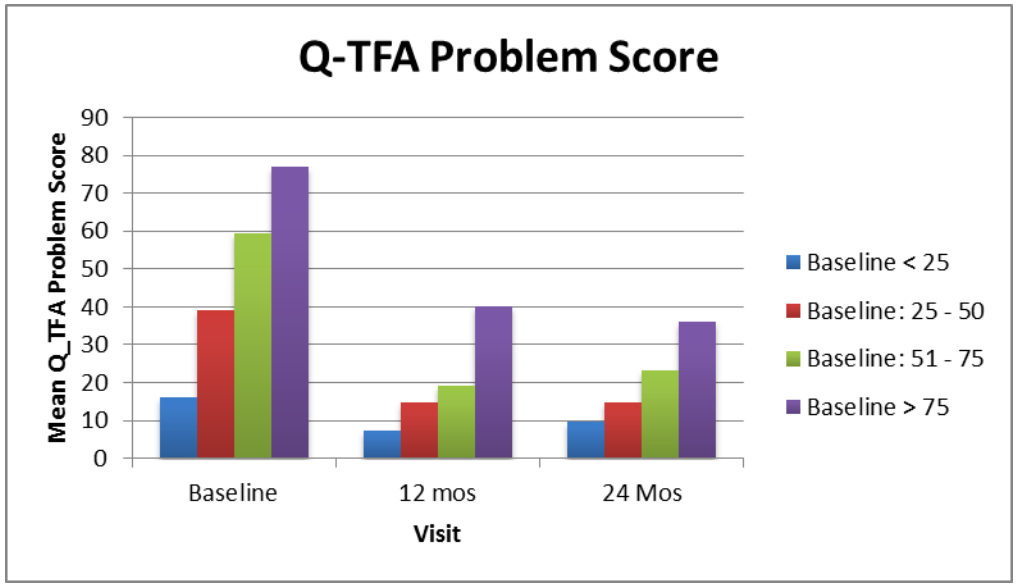

Figure 7: Mean Q-TFA Problem Score by Visit

Risks (Safety) Analysis

Adverse Events (AEs) were captured from the enrollment of the subject and until the subject had the 24 month visit. An Adverse Event 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 Adverse Events 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
- Pre-specified AEs
- Superficial Infection
- Deep Infection
- Pain
- Mechanical complication of OPRA
- Skeletal fracture
- Loosening of OPRA
- Other non-pre-specified 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
- Was a congenital anomaly/birth defect

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 been demonstrated, was improbable, but not impossible.
- Possibly Related: A direct cause and effect relationship between the AE and the OPRA Implant System was not been 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 complication 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 or re-amputation has been reported with the OPRA Implant System.

Table 5 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 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 with 4 events reported in 4 subjects.

Table 5: 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 and infestations	**44**	**31 (60.8%)**
Infection	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%)
Fracture	3	3 (5.9%)
Injury*	4	4 (7.8%)
Joint injury	1	1 (2.0%)
Post procedural haematoma	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 shown in the table above, a total of 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 101 treatment emergent AEs, 47 AEs reported by 28 (55%) subjects were considered serious. The most frequent SAEs were:

- Infection, reported by 8 (16%) subjects with 10 events, whereof:
  - Superficial infection, reported by 4 (8%) subjects with 4 events.

- Deep infection, reported by 4 (8%) subjects with 6 events.

- Secondary surgical intervention (including reoperation, component replacement/revision, removal): 13 events (25.5%), specific to implant removal (3 implants removed during the study and 1 shortly after the study, giving 4 events in 4 patients; 8%).

Table 6 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 treat 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 6 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 6 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 5 are captured in Table 6; 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 6. Subjects with treatment emergent Adverse Events over time (Safety Population)

Adverse 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 (%); None[x]	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							
Myocardial infarction; None[x]							
Pulmonary emboli; None[x]							
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
[x] None; denotes that no events were reported in these categories shaded in dark grey in the table.

The risks associated with this device should be compared to the amputated population as a whole. For instance the incidence of pain, skin sores and discomfort from a socket suspended prosthesis is in the order of 50% during a four week period.[2] For the OPRA Implant System 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. The incidence of revision requiring removal of the entire OPRA Implant system was 8%, well in line with limb salvage procedures, which are often considered as an alternative to transfemoral amputation on patient with distal bone tumours.[1, 2]

In summary, the OPRA Implant study showed the following results for the OPRA Implant System:

- Increased use and function at 12 and 24 months relative to the use of previous prosthetics systems at Baseline. This is supported by the primary as well as secondary and tertiary efficacy variables. This information was further presented in the Figures 4-7, above.
- Approximately 89% of the legs included in the study reached full loading of the OPRA Implant System by the end of the study; 24 months.
- The prespecified AEs, outlined above, were the most common AEs.

The following have been identified as known risks of using the OPRA device:

- The most frequently reported AEs were superficial infections, which occurred at a frequency of 54.9%

- Serious Adverse Events resulting in surgical intervention were dominated by treatable mechanical failure.
- 4 out of the 51 (8%) patients had their implants removed due to loosening or persistent pain.

In a post market survey of subjects in the OPRA Implant study, 35 of 45 subjects responded to the question, "Do you think the advantages outweigh the disadvantages when you add up surgeries and rehabilitation and possible complications (e.g., complications as abutment changes, superficial infections, etc.)?" Responses were provided on a 1 to 5 scale, 5 the most positive response and 1 the least. The 35 subjects averaged 8.5 years (range 4.9 to 13.1) since the 2nd surgery, and gave responses for the 5 year postoperative interval as well as for the time at which the survey was completed. Thirty-one subjects (89%) gave a score of 5 for both time points, 2 (6%) subjects responded with a 4 at both time points, 1 (3%) subject responded with a 4 at the first time point and a 5 at the second time point, and 1 (3%) subject responded with a 2 at both time points.

Relevant Clinical Literature Regarding OPRA

The following three articles have been published based on the same patient population as the OPRA Implant Study or portions thereof. Please note that the term osseointegration is used in the literature but is a claim that cannot be supported by the sponsor at this time.

The study performed by Nebergall et al.[5] 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 in Section 4.1.

Tranberg et al.[3] included post-operative data showing 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 transfemoral 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 lumbar biomechanics and could contribute to reducing the risk of further problems with low back pain.

Hagberg et al.[4] presented the first report on prospective outcomes for individuals treated with bone-anchored transfemoral amputation prostheses (OI-prostheses) using the method of osseointegration. The aim was to analyze general and condition-specific health related quality of life (HRQL) at 2-year follow-up as compared to the preoperative situation. The study population consisted of the first 18 consecutively treated patients (8 male/10 female, mean age 45 years) in the OPRA investigation with amputations mainly caused by trauma and tumor. At inclusion, the mean time since the amputation was 15 years (10 months - 33 years). Three of the 18 patients were not prosthetic users (wore a prosthesis at least once a week) prior to this study. Thirteen (13) of the 15 who wore prostheses used a vacuum socket prosthesis, and two used a silicon liner with their socket prosthesis. Two self-report questionnaires were answered preoperatively and at follow-up: the SF-36 Health Survey (SF-36) and the Questionnaire for persons with a Transfemoral Amputation (Q-TFA). At follow-up 17/18 patients used the OI-prosthesis; one did not due to pain and loosening of the implant. It was determined that this implant was loose, possibly as a result of osteoporosis from being an amputee for 32 years. However, this patient requested to be treated again, and in 2003, the surgical procedures were repeated, with an individually designed rehabilitation protocol. Two patients experienced superficial infections at the skin penetration sites, for which they had to temporarily abstain from prosthesis use, but it was maintained that infection was not a significant event in this study. Four scales of the SF-36 (Physical Functioning, Role Functioning Physical, Bodily Pain and Physical Component Score) and all four scores of Q-TFA (Prosthetic Use, Prosthetic Mobility, Problems and Global Health) were statistically significantly improved at follow-up showing superior general physical HRQL, increased prosthetic use, better prosthetic mobility, fewer problems and better overall daily activities. Two-year follow up data on the Health-Related Quality of Life (HRQL) of the first 18 consecutively treated patients under this prospective study protocol demonstrated that most (17 out of 18 subjects) of the individuals treated with the OPRA TFA OI-prosthesis experienced considerable improvement of their general well-being, as well as condition-specific well-being, compared to before the implant surgery. Based on the experience from these 18 prospectively followed patients, the success rate for the OPRA device at 2 years post-implantation was 94%.

Conclusions drawn from the clinical literature

The clinical experience presented indicates that osseoanchored devices lead to an acceptable level of patient satisfaction and are associated with an acceptable complication risk level. Studies have shown increased prosthetic use, better prosthetic mobility, fewer problems and better overall daily activities. There is a definite risk of infection. However, the clinical evidence shows that use of osseoanchored devices leads to manageable infectious complications in transfemoral amputees. Further, longer-term post-marketing data supports the findings from the OPRA Implant study and supports a positive benefit/risk assessment.[6]

The reported clinical experience with use of the OPRA Implant System confirmed associated improvements in patient comfort, function and quality of life. The cumulative implant success rate (defined as lack of implant removal or revision) was over 90 % at 2 years follow-up.

XI. 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 investigator. The clinical investigator had no disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. RISK/PROBABLE BENEFIT ANALYSIS

The OPRA device is an implant system for direct skeletal anchorage of amputation prostheses. The OPRA device is indicated for patients with transfemoral amputation due to trauma or cancer and who have rehabilitation problems with or cannot use a conventional socket prosthesis. Therefore, OPRA constitutes a rehabilitation alternative for transfemoral amputees (TFA) when treatment with socket prostheses is insufficient. Based on the clinical dataset, patients who have serious problems using a socket prostheses have the largest probable benefit.

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 (OI-prostheses) were developed as an alternative to conventional socket prostheses and are intended to offer the TFA patient several benefits 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 subscores;
- Improved quality of life as demonstrated by the Q-TFA;
- Reduced socket related soft tissue problems;

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

- 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.

Please note that while bilateral subjects were included in the study, their numbers were very low (n=6). The outcomes in bilateral patients are therefore, unknown and study results cannot support any definitive conclusions regarding this subset patient population. It is possible these patients may not see all the probable benefits as the unilateral subjects.

There exists the possibility that the OPRA device, because it is directly attached to the residual bone via surgical implantation into the femur, may not optimally stabilize the pelvis/align the stump in some subjects when compared to a socket prosthesis which can undergo slight adjustments. However, this can be addressed with individualized prosthetic components, and appropriate physical rehabilitation and activity management.

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for "patients who have transfemoral or trans-tibial amputation due to trauma or cancer and who cannot use a conventional socket prosthesis." It was modified for the HDE approval because of the clinical dataset provided. Specifically, the statement was clarified to address patients who have rehabilitation problems with or cannot use conventional socket prostheses, as this further explains why the prosthesis is not able to effectively be used.

Based on data from the OPRA Implant Clinical Investigation, the Agency believes that the probable benefits as outlined previously outweigh the risks associated with OPRA device as the physical and prosthetic advantages have led to improvement in candidates' comfort, function and quality of life. Frequent adverse events experienced by users of the OPRA device have generally been temporary in nature. Notably, in two out of four cases of implant failure, the subjects elected to have the device re-implanted. Probable risks of the OPRA device can be effectively managed by individualized prosthetic components, as well as appropriate physical rehabilitation, activity and health management. Therefore, the Agency concludes that the probable benefits outweigh the risks associated with this device.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Orthopedics and Rehabilitation Devices Panel because no specific clinical issues arose that required panel input. The potential adverse events are clearly defined by the clinical dataset. Therefore, it was determined that this application need not be submitted to the advisory panel.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the Osseoanchored Prostheses for the Rehabilitation of Amputees will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on July 16, 2015.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

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

Postapproval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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