

## SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

### I. GENERAL INFORMATION

Device Generic Name:	Hyaluronic Acid, Intraarticular
Device Trade Name:	EUFLEXXA® (1% Sodium Hyaluronate)
Applicant's Name and Address:	Ferring Pharmaceuticals, Inc. 4 Gatehall Drive, 3rd Floor Parsippany, New Jersey 07054
Date(s) of Panel Recommendation:	Not applicable (NA)
Premarket Approval Application (PMA) Number:	P010029/S008
Date of FDA Notice of Approval:	October 11, 2011
Expedited:	NA

The original PMA application P010029 for Nuflexxa (1% Sodium Hyaluronate) was approved on December 3, 2004. That device is a three injection regimen which is indicated for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen). Preclinical data from the original application are applicable to the current PMA supplement for EUFLEXX® (1% Sodium Hyaluronate) and are therefore incorporated by reference. Please refer to the SSED for P010029 for additional supporting documentation. You may obtain a copy of the SSED via the CDRH website at [http://www.accessdata.fda.gov/cdrh\\_docs/pdf/P010029b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf/P010029b.pdf). Written requests for copies can be obtained from The Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857 under Docket # 98M-0217 .

### II. INDICATIONS FOR USE

EUFLEXXA is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen).

### III. CONTRAINDICATIONS

- Do not use EUFLEXXA to treat patients who have a known hypersensitivity to hyaluronan preparations.
- Do not use EUFLEXXA to treat patients with knee joint infections, infections or skin disease in the area of the injection site.

### IV. WARNINGS AND PRECAUTIONS

#### WARNINGS

- Mixing of quaternary ammonium salts such as benzalkonium chloride with hyaluronan solutions results in formation of a precipitate. EUFLEXXA® should not be administered through a needle previously used with medical solutions containing benzalkonium chloride. Do not use disinfectants for skin preparation that contain quaternary ammonium salts.
- Do not inject intravascularly because intravascular injection may cause systemic adverse events.

## PRECAUTIONS

### GENERAL

- Patients having repeated exposure to EUFLEXXA® have the potential for an immune response; however, this has not been assessed in humans.
- Safety and effectiveness of injection in conjunction with other intra-articular injectables, or into joints other than the knee has not been established.
- Remove any joint effusion before injecting.
- Transient pain or swelling of the injected joint may occur after intra-articular injection with EUFLEXXA®.
- Do not use after expiration date.
- Protect from light.
- Do not re-use—dispose of the syringe after use.
- Do not use if the blister package is opened or damaged.

### Information for Patients

- Transient pain and/or swelling of the injected joint may occur after intra-articular injection of EUFLEXXA®.
- As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged (i.e., more than 1 hour) weight-bearing activities such as jogging or tennis within 48 hours following intra-articular injection.
- The safety of repeated treatment cycles of EUFLEXXA® has been established up to 1 year.

### Use in Specific Populations

- **Pregnancy:** The safety and effectiveness of EUFLEXXA® have not been established in pregnant women.
- **Nursing Mothers:** It is not known if EUFLEXXA® is excreted in human milk. The safety and effectiveness of EUFLEXXA® have not been established in lactating women.
- **Children:** The safety and effectiveness of EUFLEXXA® have not been demonstrated in children.

## V. DEVICE DESCRIPTION

### DESCRIPTION

EUFLEXXA® is a viscoelastic, sterile solution of highly purified, high molecular weight (2.4-3.6 million daltons) hyaluronan (also known as sodium hyaluronate) in phosphate-buffered saline. EUFLEXXA® is a very highly purified product extracted from bacterial cells. It is a polysaccharide consisting of a repeating disaccharide of N-acetylglucosamine and sodium glucuronate, linked by alternating  $\beta \rightarrow 1, 3$  and  $\beta \rightarrow 1, 4$  glycosidic bonds.

Table 1. Each syringe of EUFLEXXA contains:

CONTENT	
Each 1 ml of EUFLEXXA contains:	
Sodium hyaluronate	10mg
Sodium chloride	8.5 mg
Disodium hydrogen phosphate dodecahydrate	0.56 mg
Sodium dihydrogen phosphate dihydrate	0.05 mg
Water for injection	q.s.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

For patients who have failed to respond adequately to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen), alternative practices and procedures include nonsteroidal anti-inflammatory drugs (NSAIDs); intra-articular injection of corticosteroid; avoidance of activities that cause joint pain; exercise; physical therapy; weight loss; and removal of excess fluid from the knee. For patients who have failed the above treatments, surgical interventions such as arthroscopic surgery and total knee replacement are also alternative treatments.

## **VII. MARKETING HISTORY**

Sodium hyaluronate, manufactured by Bio-Technology General (Israel) Ltd. (BTG) has been marketed as Ophtha and 1% NaHA solution. Since April 1993 the product has been marketed as BioLon for use in eye surgery. In June 1995, BioLon was approved as a medical device by MDC (Medical Device Certification), a notified body of the European Community, and a CE mark was issued. In July 1998, BioLon received PMA approval by the Center for Devices and Radiological Health for use in ophthalmology.

BioLon, Ophtha, and 1% NaHA have never been withdrawn from marketing for any reason related to safety or effectiveness of the device.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

a. The most common adverse event related to EUFLEXXA<sup>®</sup> injections reported in the clinical studies are the following:

- Arthralgia
- Back pain
- Pain in extremity
- Musculoskeletal pain
- Joint swelling

b. Potential Adverse Events

The following adverse events are among those that may occur in association with intra-articular injections

- Arthralgia
- Joint swelling
- Joint effusion
- Injection site pain
- Arthritis

There were also reports of the incidence of upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, injury, headache, diarrhea, nausea, pain, cough, and hypertension.

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

## **IX. Summary of Preclinical Studies**

This supplement presented clinical data to support approval of a new indication for use. Because no change in product manufacturing or specification was proposed, the supplement did not contain any manufacturing information or preclinical testing. Instead, the data presented in original P010029 were sufficient to support the new proposed indication for use.

## **X. SUMMARY OF PRIMARY CLINICAL STUDIES**

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of 3 weekly injections of EUFLEXXA up to 26 weeks for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics e.g., acetaminophen. Data from this clinical study were the basis for the PMA approval decision.

The study was a prospective, multi-center, randomized, double-blind, two-arm (parallel group) clinical study conducted at 37 sites in the United States. Five hundreds and eighty eight (588) patients were randomized to receive either a single intra-articular (IA) injection of EUFLEXXA (n=293) or Phosphate buffered saline (PBS) (n=295) between October 2006 to December 2007 as part of this study. Neither the patients nor the clinical observers knew the patients' treatment allocations.

#### **A. Study Design:**

The study was conducted in two phases:

- An initial treatment phase to evaluate the safety and efficacy of a three weekly IA doses of 2 mL of either EUFLEXXA or saline placebo injected into the knee from baseline through 26 weeks.
- An open-label repeat treatment phase of an additional three 2-mL injections of EUFLEXXA for another 26 weeks after the initial treatment phase was also assessed for safety.

#### **Efficacy Parameter**

Pain scores on the 50-foot walk test

The primary objective of the trial was to compare EUFLEXXA and placebo with respect to the change in the mean pain scores on the 50-foot walk test, measured on a 100-mm horizontal VAS (from 0 mm = no pain to 100 mm = extreme pain), from baseline (Week 0, first injection) to the final study visit (Week 26) for the ITT population. The null hypothesis ( $H_0$ ) was that the change from baseline between the two treatment groups is equal, and the alternative hypothesis ( $H_A$ ) was that change from baseline between the two treatment groups is different. The study was considered successful if it demonstrated that the change from baseline in the two treatment groups was significantly different and that the improvement with EUFLEXXA (a greater decrease in the mean pain scores) was greater than that with placebo. In mathematical terms, the hypothesis to be tested for the primary efficacy variable was:

$H_0: \mu_p = \mu_E$  versus  $H_A: \mu_p \neq \mu_E$

where  $\mu_E$  was the mean change from baseline to Week 26 for EUFLEXXA, and  $\mu_p$  was the mean change from baseline to Week 26 for placebo.

#### **Device Treatment (Use) Test Product, Dose and Mode of Administration, Batch Number:**

EUFLEXXA (20 mg/2 mL 1% sodium hyaluronate) in a disposable, prefilled, single-dose, glass syringe: 2 mL injected into the target knee once weekly (Visit 2/Week 0, Visit 3/Week 1, and Visit 4/Week 2)  
Duration of Treatment: 3 weeks

**Reference Therapy, Dose and Mode of Administration, Batch Number:** Placebo (phosphate-buffered saline) in a disposable, prefilled; glass syringe: 2 mL injected into the target knee once weekly (Visit 2/Week 0, Visit 3/Week 1, and Visit 4/Week 2)

#### **Initial 26 Week Multicenter Study and an open-label repeat treatment**

This was a multicenter, randomized, double-blind trial evaluating the efficacy and safety of EUFLEXXA<sup>®</sup>, as compared with placebo (saline comparator), in subjects with chronic osteoarthritis of the knee followed by an open labeled safety extension study. The intervention consisted of three weekly injections of study device into the target knee, with scheduled follow-up evaluations during the 26 weeks following the first injection. In the extension phase subjects received three weekly injections of EUFLEXXA<sup>®</sup> into the target knee with follow-up evaluation up to 52 weeks for the evaluation of safety.

#### **1. Clinical Inclusion and Exclusion Criteria**

1.1.1 Inclusion	Exclusion
<ol style="list-style-type: none"> <li>1. Men or women <math>\geq</math> 40 years of age</li> <li>2. Chronic OA of target knee confirmed by ACR Criteria (see Appendix 5 of the Clinical Study Protocol in Appendix 16.1.1)</li> <li>3. Pain due to OA in target knee that had been present for at least 6 months, with a moderate to severe pain score of 41 to 90 mm recorded on a 100-mm VAS immediately following a 50-foot walk</li> <li>4. A bilateral standing AP x-ray confirming grade 2 or 3 OA of the target knee by the Kellgren and Lawrence Grading Scale (see Appendix 4 of the Clinical Study Protocol, Appendix 16.1.1) and obtained within 6 months prior to the screening visit</li> <li>5. Ability and willingness to use <i>only</i> acetaminophen as the analgesic (rescue) study medication <ul style="list-style-type: none"> <li>• The acetaminophen dose was not to exceed 4 grams (4000 mg)/day.</li> <li>• If the subject had known chronic liver disease, the maximum dose of acetaminophen was not to exceed 2 grams (2000 mg)/day.</li> <li>• The subject had to be willing and able to discontinue acetaminophen at least 24 hours prior to all study-specific visits.</li> <li>• The provided study-specific acetaminophen was only to be used for knee pain.</li> </ul> </li> <li>6. Ability to perform procedures required of the pain index evaluations (unassisted walking for a distance of 50 feet on a flat surface and going up and down stairs)</li> <li>7. Willingness and ability to complete efficacy and safety questionnaires and the ability to read and understand study instructions</li> <li>8. Signed study-specific subject ICF</li> <li>9. <i>Allowed Study Exceptions</i></li> </ol> <p>Enrollment was also permitted for the following subjects:</p> <ol style="list-style-type: none"> <li>1. Subjects having x-ray confirmation of OA in the nontarget (contralateral) knee were allowed to be enrolled in the trial as long as the target knee was the more</li> </ol>	

<p>symptomatic knee and met the criteria listed above. Pain in the nontarget knee had to be limited to &lt;40 mm following the 50-foot walk test at screening.</p> <ol style="list-style-type: none"> <li>2. If topical heat or ice packs were used for pain relief, they had to be discontinued at least 24 hours before study-specific pain evaluations.</li> <li>3. Acetylsalicylic acid (aspirin) at a maximum dose of 325 mg/day for prophylaxis to prevent thrombosis was allowed.</li> <li>4. Nonprescription nutraceuticals (e.g., glucosamine and chondroitin), topical analgesics, and nasal or inhaled corticosteroids were allowed if the dosage had been stable for at least 1 month prior to the screening visit and the identical regimen continued throughout the study period.</li> <li>5. Nonpharmacological treatments (physical therapy, acupuncture, osteopathic, and chiropractic manipulations) were allowed if the treatment had been stable for at least 1 month prior to study entry and there was no plan to change the frequency during the course of the study.</li> </ol>	
	<p style="text-align: center;"><b>Exclusion Criteria</b></p> <p>The presence of <i>any</i> of the following criteria excluded a subject from enrollment:</p> <ol style="list-style-type: none"> <li>1. Any major injury (including sports injuries) to the target knee within the 12 months prior to the screening visit</li> <li>2. Any surgery to the target knee within the 12 months prior to the screening visit, or surgery to the contralateral knee or other weight-bearing joint if it would have interfered with knee assessments</li> <li>3. Articular procedures such as transplants or ligament reconstruction to the target knee within 12 months</li> <li>4. Inflammatory arthropathies such as rheumatoid arthritis, lupus arthropathy, or psoriatic arthritis</li> <li>5. Gout or calcium pyrophosphate (pseudogout) diseases of the target knee that had flared within the 6 months prior to the screening visit</li> <li>6. X-ray findings of acute fractures, severe loss of bone density, avascular necrosis, and/or severe bone or joint deformity in the target knee</li> <li>7. Osteonecrosis of either knee</li> <li>8. Fibromyalgia, pes anserine bursitis, lumbar radiculopathy, and/or neurogenic or vascular claudication</li> <li>9. Significant anterior knee pain due to diagnosed isolated patella-femoral syndrome or chondromalacia in the target knee</li> </ol>

10. Significant target knee joint, infection or skin disorder infection within the 6 months prior to study enrollment
11. Symptomatic OA of the hips, spine, or ankle, if it would have interfered with the evaluation of the target knee
12. Known hypersensitivity to acetaminophen, EUFLEXXA, or phosphate-buffered saline solution
13. Women of childbearing potential who were pregnant, nursing, or planning to become pregnant, or who did not agree to remain on an acceptable method of birth control throughout the entire study period
14. History of recurrent severe allergic or immune-mediated reactions or other immune disorders
15. Vascular insufficiency of lower limbs or peripheral neuropathy severe enough to have interfered with the study evaluation
16. Current treatment, or treatment within the 2 years prior to the screening visit, for any malignancy, unless specific written permission was provided by the sponsor (excluding basal cell or squamous cell carcinoma of the skin)
17. Active liver disease based on liver profile of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and conjugated bilirubin >2 times the upper limit of normal
18. Renal insufficiency based on serum creatinine >2.0 mg/dl,
19. Any clinically significant laboratory value that the investigator felt, based on clinical history, might have affected the study evaluation
20. Any intercurrent chronic disease or condition that might have interfered with the completion of the 6-month (or 12-month) follow-up of the study, such as liver disease, severe coronary disease, drug abuse, disordered mental state, or other clinically significant condition
21. Current alcoholism and/or any known current addiction to pain medications
22. Any clinically significant finding that would have placed the subject at health risk, impacted the study, or affected completion of the study
23. Any psychiatric illness that would have prevented comprehension of the details and nature of the study
24. Participation in any experimental device study within 6 months prior to the screening visit, or participation in an experimental drug study within 1 month prior to the screening visit

**Removal of Subjects, from Therapy or Assessment**

Every subject had the right to refuse further participation in the study at any time without providing a reason. A subject's participation was required to terminate immediately upon his/her request. If, at the time of refusal, the investigational product had already been administered, the subject was advised to complete the follow-up safety investigations for the

	<p>final visit/Week 26.</p> <p>The investigator may have withdrawn a subject from the study at any time after first discussing the reason with the sponsor. If a subject developed conditions during the course of the study that would have prevented enrollment in the study according to the exclusion criteria, the withdrawal potential for the subject had to be discussed with the sponsor.</p> <p>In addition, a subject was required to be withdrawn from the study for any of the following reasons:</p> <ul style="list-style-type: none"> <li>• The investigator felt the subject's safety was at risk.</li> <li>• Culture of synovial fluid aspirate was positive.</li> <li>• There was a change in the status of the subject's knees that rendered his/her study data un-assessable (e.g., surgical procedure, steroid injections, presence of pain in the contralateral knee that limited his/her ability to undergo the WOMAC procedures).</li> <li>• The subject withdrew consent.</li> </ul> <p>Subjects enrolled in the study were not permitted to re-enroll for a second time in the study.</p>
--	--

2. Follow-up Schedule

Table 2. SCHEDULE for procedures and evaluations

	Visit 1/Week -3 to -1	Visit 2/Week 0	Telephone call	Visit 3/Week 1	Telephone call	Visit 4/Week 2	Telephone call	Visit 5/Week 3	Visit 6/Week 6	Visit 7/Week 12	Visit 8/Week 18	Visit 9/Week 26	Visit 10/Week 27	Visit 11/Week 28	Telephone call	Visit 12/Week 41	Visit 8/Week 13
Procedure	Screen	Baseline/Randomization	2-3 days post inject		2-3 days post inject		2-3 days post inject					Final			2-3 days post inject		
Informed Consent	X																
Inclusion/Exclusion <sup>1</sup>	X																
Physical exam	X																
Medical/orthopedic history	X																
Dx of moderate OA	X																
Bilateral X-rays <sup>2</sup>	X																
Safety labs <sup>3</sup>	X																
Vital signs	X	X		X		X		X	X	X	X	X	X	X		X	X
WOMAC by VAS	X	X		X		X		X	X	X	X	X	X	X		X	X
Kellgren and Lawrence	X																

Antibody testing <sup>4</sup>		X		X		X		X	X	X	X	X	X	X	X	X
Exam of Target knee <sup>5</sup>	X	X		X		X		X	X	X	X	X	X		X	X
Randomize subject		X		X		X		X	X	X	X	X	X		X	X
Aspirate/inject knee <sup>6</sup>		X		X		X		X	X	X	X	X <sup>7</sup>	X	X	X	X
Observe knee 5 min post injection		X		X		X		X	X	X	X	X <sup>7</sup>	X	X	X	X
Adverse events		X		X		X		X	X	X	X	X	X		X	X
Concomitant & Rescue medications	X	X		X		X		X	X	X	X	X	X		X	X
GI Assessment by VAS	X															
Patient's Utility by VAS		X		X		X		X	X	X	X	X	X		X	X
SF-36 Health Survey <sup>8</sup>	X	X								X		X				X
5 questions for AE assessment			X			X										

- 1 Inclusion/exclusion should be re-evaluated prior to the first injection of the open-label extension arm
  - 2 X-ray must be within the 6 months prior to the screening visit.
  - 3 Send to local laboratory (includes complete blood count / differential and complete metabolic profile).
  - 4 Antibody testing for subgroup of subjects only (not all sites will participate).
  - 5 Exam must be done by Investigator who is blind to the subject treatment
  - 6 Injection must be done by dosing person separate from person performing knee evaluation.
  - 7 First injection in the reinjection series for open-label extension arm.
  - 8 The SF-36 Health Survey should always be performed at the beginning of the study visit.
- OA=osteoarthritis; VAS=visual analogue; vital signs=blood pressure, heart rate, and temperature.

### **3. Study Endpoints**

#### **Primary Effectiveness**

The primary efficacy variable was the change from baseline in mean target knee pain scores on the 50-foot walk test, measured on a 100-mm horizontal VAS. For the primary efficacy analysis, the analysis is based on repeated measure mixed model Analysis of Covariance (ANCOVA) from baseline through 26 weeks on mean change from baseline 50-foot walk test, measured on a 100mm horizontal VAS score improvement at 26 weeks, with weekly injection of Euflexxa for 3 weeks.

The primary endpoint was to compare EUFLEXXA and placebo with respect to the change in the mean pain scores on the 50-foot walk test, measured on a 100-mm horizontal VAS (from 0 mm = no pain to 100 mm = extreme pain), from baseline (Week 0, first injection) to the final study visit (Week 26) for the ITT population. The null hypothesis ( $H_0$ ) was that the change from baseline between the two treatment groups is equal, and the alternative hypothesis  $H_A$  was that change from baseline between the two treatment groups is different. The study was considered successful if it demonstrated that the change from baseline in the two treatment groups was significantly different and that the improvement with EUFLEXXA (a greater decrease in the mean pain scores) was greater than that with placebo. In

mathematical terms, the hypothesis to be tested for the primary efficacy variable was:

$H_0: \mu_p = \mu_E$  versus  $H_a: \mu_p \neq \mu_E$

where  $\mu_E$  was the mean change from baseline to Week 26 for EUFLEXXA, and  $\mu_p$  was the mean change from baseline to Week 26 for placebo.

The VAS scores on the 50-foot walk test were analyzed using repeated-measures, mixed-model analysis of covariance (ANCOVA) model, with no data imputation. The model included the following factors: baseline pain score on the 50-foot walk test as a covariate, study center, treatment group, study week, and treatment group-by-study week interaction. Study center was classified as a random factor, and study week as a repeated measure. The interactions between study center and treatment group and between the covariate and treatment group were also included in the model. Any of these interaction terms not found to be statistically significant, with a p-value >0.10, were removed from the final model. If the interaction between study center and treatment group was found to be statistically significant, a review of the data was to be performed to determine the cause of the statistical significance and the appropriateness of pooling data from all study centers. The repeated-measures analysis with the mixed-effect linear model employed a suitable covariance structure for each analysis. The covariance structure was selected separately for each outcome variable. Based on the Akaike Information Criterion, the best covariance structure was selected from the following: unstructured, compound symmetry, compound symmetry with heterogeneous variances, autoregressive order 1, or autoregressive order 1 with heterogeneous variances. Only those covariance structures that resulted in convergence in the estimation of the statistical model were selected.

#### Secondary Effectiveness/Safety

Secondary efficacy variables included the change in WOMAC pain, disability, and joint stiffness VAS scores; change in SF-36 Health Survey scores for the physical functioning and pain domains; change in Patient Global Assessment VAS scores; OARSI responder rate; and number of tablets of study-specific acetaminophen (rescue medication).

#### Success/Failure Criteria

Study success will be defined as:

Regarding the success criteria of the study, there should be a statistically significant as well as the clinically meaningful difference between the two treatment groups using the least squares means obtained for the repeated measures analysis.

#### B. Accountability of PMA Cohort

##### Data Sets Analyzed

Table 2 summarizes the populations analyzed for the randomization/treatment phase of the study. The safety population was composed of 588 subjects, the same as the number randomized. The ITT and evaluable populations were composed of 586 and 518 subjects, respectively. Both the EUFLEXXA and placebo groups had similar percentages of subjects in each analysis population.

Table 3. Study Populations (Randomized Subjects)

Population	Saline N = 295 n (%)	EUFLEXXA N = 293 n (%)	All Treatments N = 588 n (%)
Safety	295(100)	293(100)	588(100)
Intent-to-treat (ITT)	295(100)	291 (99.3)	586 (99.7)
Evaluable	261 (88.5)	257 (87.7)	518(88.1)

N = number of subjects in a given treatment group for the population analyzed; n = number of subjects; (%) = percentage of subjects based on N.

Note: The safety population consisted of all randomized subjects who had received at least one injection of study device. The ITT population consisted of all safety subjects who had a baseline evaluation and at least one post-baseline evaluation. The evaluable population consisted of all ITT subjects who had completed the full treatment period and had no important protocol violations. Important protocol violations were violations that resulted in the subject's discontinuation from the study.

### **C. Study Population Demographics and Baseline Parameters**

#### Demographic and Other Baseline Characteristics

The overall mean (SD) age was 61.6 (10.50) years; and the majority of the subjects were female (63.1%) and Caucasian (78.1%). The mean (SD) BMI was 32.70 (7.446) kg/ml. The two treatment groups were similar with respect to demographic characteristics. The demographic characteristics of the ITT and evaluable populations were similar to those of the safety population.

Table 4. Demographic Characteristics (Safety Population)

Characteristic Statistic	Saline N = 295	EUFLEXXA N = 293	All Treatments N = 588	P- value
Sex-n (%)				>0.999
Male	109(36.9)	108(36.9)	217(36.9)	
Female	186(63.1)	185(63.1)	371 (63.1)	
Age (years)				0.068
N	295	293	588	
Mean	60.8	62.5	61.6	
SD	10.31	10.62	10.50	
Median	60.5	61.9	61.2	
Minimum	40	41	40	
Maximum	90	90	90	
Race - n (%)				0.772
Caucasian	228 (77.3)	231 (78.8)	459(78.1)	
African American	33(11.2)	26 (8.9)	59(10.0)	
Asian	5(1.7)	5(1.7)	10(1.7)	
Hispanic	25 (8.5)	29 (9.9)	54 (9.2)	
Other	4(1.4)	2 (0.7)	6(1.0)	
Weight (kg)				0.356
N	287	288	575	
Mean	92.8	91.0	91.9	
SD	21.68	21.95	21.81	
Median	90.7	87.7	89.4	
Minimum	46	49	46	
Maximum	171	190	190	
BMI(kg/m <sup>2</sup> )				0.307
N	286	288	574	
Mean	33.03	32.36	32.70	
SD	7.44	7.44	7.44	
Median	31.59	31.33	31.49	
Minimum	16.3	18.7	16.3	
Maximum	63.0	59.8	63.0	

N = number of subjects in a given treatment group for the population analyzed; n = number of subjects; (%) = percentage of subjects based on N; SD = standard deviation; BMI = body mass index.

Note; Age was calculated as: age = (date of informed consent - date of birth) / 365.25. BMI was calculated as: BMI = weight / (height \* height). The reported p-values were obtained from a Wilcoxon rank-sum for continuous variables. For categorical variables, the reported p-values were obtained from a Fisher's exact test for variables with two categories, and from a Mantel-Haenszel chi-square test for general association for variables with more than two categories.

#### **D. Safety and Effectiveness Results**

##### **1. Safety Results**

The analysis of safety was based on the (list type) cohort of 588 patients, available for the 14 months evaluation. The key safety outcomes for this study are presented below in tables 1 to 2.

#### **ADVERSE EFFECTS THAT OCCURRED IN THE PMA CLINICAL STUDY:**

Adverse event

Table 5 shows the treatment-emergent adverse events (TEAE) by preferred term with an incidence of  $\geq 2\%$  among treatment groups.

Table 5: Treatment-Emergent Adverse Events (TEAE) by Preferred Term with an Incidence of  $\geq 2\%$  among the Treatment Groups (Safety Population)

System Organ Class Preferred Term	26 Week FLEXX Study (Core)			Extension Study 3 Repeat Injections for 52 Weeks*
	All Treatments N = 588 n (%)	SALINE N = 295 n (%)	EUFLEXXA® N = 293 n (%)	EUFLEXXA® N = 219 n (%)
Any TEAE	326 (55.4)	169 (57.3)	157 (53.6)	96 (43.8)
Musculoskeletal and connective tissue disorders				
Arthralgia	62 (10.5)	35 (11.9)	27 (9.2)	19 (8.7)
Back pain	23 (3.9)	11 (3.7)	12 (4.1)	6 (2.7)
Pain in extremity	13 (2.2)	10 (3.4)	3 (1.0)	3 (1.4)
Musculoskeletal pain	10 (1.7)	4 (1.4)	6 (2.0)	2 (0.9)
Osteoarthritis	9 (1.5)	7 (2.4)	2 (0.7)	0
Joint Swelling	8 (1.4)	4 (1.4)	4 (1.4)	6 (2.7)
Infections and infestations				
Upper respiratory tract infection	23 (3.9)	11 (3.7)	12 (4.1)	6 (2.7)
Nasopharyngitis	17 (2.9)	13 (4.4)	4 (1.4)	10 (4.6)
Sinusitis	16 (2.7)	10 (3.4)	6 (2.0)	5 (2.3)
Urinary tract infection	12 (2.0)	6 (2.0)	6 (2.0)	3 (1.4)
Injury, poisoning, and procedural complications				
Injury	17 (2.9)	9 (3.1)	8 (2.7)	9 (4.1)
Nervous system disorders				
Headache	17 (2.9)	11 (3.7)	6 (2.0)	3 (1.4)
Gastrointestinal disorders				

Diarrhea	14 (2.4)	2 (0.7)	12 (4.1)	3 (1.4)
Nausea	12 (2.0)	7 (2.4)	5 (1.7)	4 (1.8)
Respiratory, thoracic, and mediastinal disorders				
Cough	10 (1.7)	3 (1.0)	7 (2.4)	3 (1.4)
Vascular disorders				
Hypertension	18 (3.1)	5 (1.7)	13 (4.4)	1 (0.5)

\*Treatment group for repeat study are for subjects who received EUFLEXXA® in both the core and extension (219 out of 433).

N = number of subjects in a given treatment group for the population analyzed; n = number of subjects reporting at least one adverse event within system organ class/preferred term; (%) = percentage of subjects based on N; TEAE = treatment-emergent adverse event.

Note: An adverse event was counted as a TEAE if it was either not present at baseline (prior to the first dose of double-blind study device) or present at baseline but increased in severity during the treatment period.

### 1. Safety Results:

Initial study during the initial 26 weeks

During the randomization/treatment phase, 326 (55.4%) subjects in the safety population experienced 742 TEAEs. The proportion of subjects reporting TEAEs was generally similar in the EUFLEXXA and placebo groups (53.6% and 57.3%, respectively). The most common preferred term of TEAE was arthralgia (10.5% of all subjects). Thirty (5.1%) subjects experienced severe TEAEs, and the proportion within severe events was larger in the placebo group (6.4%) than the EUFLEXXA group (3.8%).

Overall, 10.4% of subjects had TEAEs considered related to study device, with comparable proportions in each treatment group (9.9% and 10.8% for EUFLEXXA and placebo, respectively). Twenty-three serious TEAEs were reported in 19 (3.2%) subjects during the study: 10 (3.4%) subjects in the EUFLEXXA group and 9 (3.1%) subjects in the placebo group. One of these events was considered related to the study device (increased redness of the left knee joint in Subject 034036 in the EUFLEXXA group). All of the serious TEAEs except one (Subject 023022 in the placebo group with pancreatic cancer) had a resolution date. One death occurred during the study: Subject 029043 in the placebo group died from injury due to a motor vehicle accident; the injury (a serious TEAE) was considered unrelated to study device. Eight (1.4%) subjects had 9 TEAEs leading to discontinuation: 3 (1.0%) subjects in the EUFLEXXA group and 5 (1.7%) subjects in the placebo group.

The incidence of abnormal and clinically significant chemistry results in each treatment group was generally small: 4% for EUFLEXXA and 3% for placebo. Less than 1% of subjects in either group had abnormal and clinically significant CBC results. No notable group differences were observed for any vital sign measurement. Fourteen EUFLEXXA subjects and 10 placebo subjects met the dual criteria for markedly abnormal vital signs. For joint examination findings at Week 26, both treatment groups had generally similar proportions of subjects with shifts from baseline to improved or worsened findings. The majority of subjects in each group showed no shift in joint examination findings from baseline to Week 26.

Extension phase from 26 to 52 weeks

During the extension phase, 43.4% (188/433) of subjects reported 377 TEAEs. Of these 43.8% (96/219) subjects receiving repeated EUFLEXXA® reported 199 TEAEs. The most frequently reported preferred

term in subjects formerly assigned to the core study EUFLEXXA<sup>®</sup> group were arthralgia (8.7%), nasopharyngitis (4.6%), injury (4.1%), upper respiratory tract infections (2.7%), joint swelling (2.7%), back pain (2.7%), and sinusitis (2.3%). Of these TEAEs 9 (4.1%) subjects had study drug related AEs classified as “Certain,” “Probable,” “Possible” or “Un-assessable.” The most common related TEAEs were arthralgia (2.3%) a joint swelling (1.4%). Table 6 shows the Study Drug Related Treatment-Emergent Adverse Events by Preferred Term with an Incidence of > 1 among Treatment Groups (Safety Population).

Twenty-one (4.8%) subjects had TEAEs considered related (possible, probable, or certain) to study device. The most frequently reported preferred term of related TEAE was arthralgia (2.8%), followed by joint swelling (1.2%), peripheral edema (0.7%), and injection site pain (0.5%). Twenty-two (5.1%) subjects reported severe TEAEs, the most common of which was arthralgia (4 subjects, 0.9%). The overall proportion of subjects with related TEAEs was generally similar between subjects who received EUFLEXXA during the core study and subjects who received placebo (4.1% and 5.6%, respectively). For former EUFLEXXA subjects, the most common related TEAEs were arthralgia (2.3%), joint swelling (1.4%), and peripheral edema (0.9%). For former placebo subjects, they were arthralgia (3.3%), joint swelling (0.9%), and injection site pain (0.9%).

No subject reported the TEAE of joint effusion during the extension phase. Ten (2.3%) subjects experienced 10 TEAEs of knee joint swelling. Six of these subjects had received EUFLEXXA during the core study, 1 of whom reported the event of injection site swelling during the core study. None of the extension phase TEAEs of joint swelling was serious or severe, but 5 were considered related to study device and 4 were ongoing at the time of reporting. Two additional subjects had 2 TEAEs of injection site swelling during the extension phase; both subjects had received placebo during the core study. The 2 events of injection site swelling were moderate in severity, and 1 was considered related to study device; both events resolved by the end of study.

No deaths occurred during the extension phase. Twelve (2.8%) subjects reported 20 serious TEAEs during the extension phase. Six of these subjects had received EUFLEXXA during the core study. All preferred terms of serious TEAEs were reported by one subject each, with the most frequently reported system organ classes being cardiac disorders; infections and infestations; respiratory, thoracic, and mediastinal disorders and surgical and medical procedures (2 subjects, 0.5% each). None of the serious TEAEs was considered related to study device, and all resolved. Two (0.5%) subjects had TEAEs leading to discontinuation from the study, 1 of whom received EUFLEXXA during the core study; both subjects had events that were considered unrelated to study device.

Table 6: Study Drug Related Treatment-Emergent Adverse Events by Preferred Term with an Incidence of > 1 among Treatment Groups (Safety Population)

System Organ Class Preferred Term	26 Week FLEXX Study (Core)			Extension Study Repeat Injection for 52 Weeks*
	All Treatments N = 588 n (%)	SALINE N = 295 n (%)	EUFLEXXA <sup>®</sup> N = 293 n (%)	EUFLEXXA <sup>®</sup> N = 219 n (%)
Any related TEAEs	61 (10.4)	32 (10.8)	29 (9.9)	9 (4.1)
Musculoskeletal and connective tissue disorders				
Arthralgia	23 (3.9)	13 (4.4)	10 (3.4)	5 (2.3)

Joint Swelling	3 (0.5)	2 (0.7)	1 (0.3)	3 (1.4)
Pain in extremity	3 (0.5)	3 (1)	0	0
Skin and subcutaneous tissue disorders				
Erythema	5 (0.9)	3 (1)	2 (0.7)	0

\*TEAEs are for subjects who received EUFLEXXA® in both the core and extension (219 out of 433).

N = number of subjects in a given treatment group for the population analyzed; n = number of subjects reporting at least 1 AE within system organ class/preferred term; (%) = percentage of subjects based on N; TEAE = treatment-emergent adverse event.

Note: Related AEs are AEs with study drug relationship classified as “Certain,” “Probable,” “Possible” or “Un-assessable.”

Twenty-three serious TEAEs were reported in 19 (3.2%) subjects during the study: 10 (3.4%) subjects in the EUFLEXXA® group and 9 (3.1%) subjects in the saline group. One of these events was considered related to the study device (increased redness of the left knee joint in the EUFLEXXA® group). Eight (1.4%) subjects had 9 TEAEs leading to discontinuation: 3 (1.0%) subjects in the EUFLEXXA® group and 5 (1.7%) subjects in the saline group.

Twelve (2.8%) subjects reported 20 serious TEAEs during the extension phase. Six of these subjects had received EUFLEXXA® during the core study. None of the serious TEAEs was considered related to study device, and all resolved. Two (0.5%) subjects had TEAEs leading to discontinuation from the study, 1 of whom received EUFLEXXA® during the core study; both subjects had events that were considered unrelated to study device.

Two subjects on saline experienced joint effusion. There were no reports of joint effusion among subjects receiving EUFLEXXA® during the core and extension phase.

## 2. Efficacy Results of the Initial 26 weeks:

### Primary endpoint

For the primary efficacy analysis, the analysis is based on repeated measure of mixed model of Analysis of Covariance (ANCOVA) from baseline through 26 weeks ((1, 2, 3, 6, 12, 18, and 26 week) on mean change from baseline 50-foot walk test, measured on a 100mm horizontal VAS score improvement at 26 weeks, with a weekly injection of Euflexxa for 3 weeks.

In the primary efficacy analysis, the EUFLEXXA® group showed a larger mean (SD) decrease in pain scores on the 50-foot walk test from baseline to Week 26 than the saline group: - 25.7 (STD. Dev.=28.85) mm versus -18.5 (STD. Dev.=32.53) mm, respectively. The group difference in least squares mean change from baseline of -6.6 mm (95% CI = -10.8 to -2.5 mm) was statistically significant (p-value = 0.002). Figure 1 depicts the adjusted mean change in pain scores on 50-foot walk test from baseline to week 26 (ITT Population).

**Table 7. The Adjusted Mean Change in Pain Scores on 50-foot Walk Test from Baseline to Week 26 (ITT<sup>a</sup> Population).**

	Change from Baseline at Week 26		Least Square Mean Difference in Changes (EUFLEXXA - saline) from Baseline <sup>b,c</sup>	2-Sided 95% Lower and Upper Bound of Confidence Interval of the Least Square Mean Difference in Changes <sup>c</sup>	2-Sided p-Value <sup>c</sup>
	Saline	EUFLEXXA			

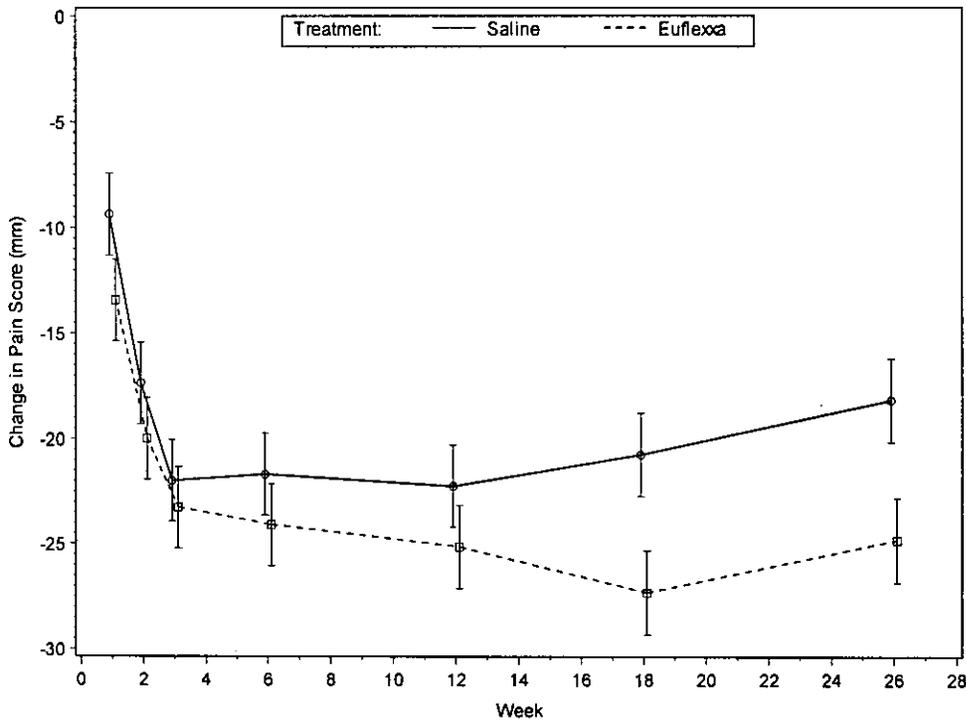
	(n=295) (SD)	(n=291) (SD)			
50-foot walk test, measured on a 100mm horizontal VAS score improvement at 26 weeks	-18.5 (32.53)	-25.7( 28.85)	-6.6 mm	-10.8, -2.5	0.002

<sup>a</sup> ITT= Intent to Treat

<sup>b</sup> Negative (-) values favor EUFLEXXA.

<sup>c</sup>The analysis is based on repeated measure mixed model Analysis of Covariance (ANCOVA) from baseline through 26 weeks on mean change from baseline 50-foot walk test, measured on a 100mm horizontal VAS score improvement at 26 weeks, with a weekly injection of EUFLEXXA for 3 weeks.

**Figure 1. Adjusted Mean Change in Pain Scores on 50-foot Walk Test from Baseline to Week 26 (ITT Population)**



#### Secondary endpoints

In the analysis of the secondary efficacy variable of OARSI responder rate using Wald chi-square test in the ITT population, the EUFLEXXA<sup>®</sup> group had a significantly larger responder rate than the saline group at Week 26 for both response based on the 50-foot walk test (66.5% versus 58.7%; odds ratio 1.4; p-value = 0.047) and response based on WOMAC A (pain) scores (61.3% versus 51.9%; odds ratio 1.5; p-value = 0.028).

#### Summary of Secondary Effectiveness<sup>a</sup> Endpoints at Week 26 – ITT Population

##### OMERACT-OARSI Response

#### Table 8. OARSI Responder Rates Using 50-foot Walk Test (ITT)

Visit Response/Statistics	Saline N=295	EUFLEXXA N=291	All Treatments N=586	Overall Comparison (2-sided 95% Lower and Upper Bound of Confidence Interval of odds ratio) <sup>c</sup>
Week 12				
No. of subjects with data	274	263	537	
Yes-n (%)	167 (60.9)	173 (65.8)	340 (63.3)	
No-n (%)	107 (39.1)	90 (34.2)	197 (36.7)	
Odds ratio <sup>a</sup> (95% CI)				1.3 (0.9, 1.8)
P-value				0.202
Week 26				
No. of subjects with data	264	254	518	
Yes-n (%)	155 (58.7)	169 (66.5)	324 (62.5)	
No-n (%)	109 (41.3)	85 (33.5)	194 (37.5)	
Odds ratio <sup>b</sup> (95%CI)				1.4 (1.0, 2.1)
P-value				0.047

OARSI = Osteoarthritis Research Society International ; ITT = intent-to-treat; N = number of subjects in a given treatment group for the population analyzed; n = number of subjects; (%) = percentage of subjects based on N; CI =confidence interval.

Note: The p-value for the odds ratio corresponds to the Wald chi-square test for EUFLEXXA versus saline with respect to OARSI responder rates from a logistic regression adjusting for treatment group and study center.

Note: A subject was considered a responder if there was high improvement in pain or function >50% and absolute change >20 nun or improvement in at least two of the three following categories: pain >20% and absolute change >10 mm, function >20% and absolute change >10 mm, and/or Patient Global Assessment >20% and absolute change >10.

a, b  $e^{(\text{Log Odds Ratio})} = 1.27$  for 12 weeks and 1.4 for 26 weeks, based on a logistic regression model  
 $(\text{Log Odds Ratio}) = \log_e \left[ \frac{\text{probability}(\text{responder}) / \text{probability}(\text{non-responder})_{\text{EUFLEXXA}}}{\text{probability}(\text{responder}) / \text{probability}(\text{non-responder})_{\text{saline}}} \right]$

c When odds ratio >1,  $[\text{probability}(\text{responder}) / \text{probability}(\text{non-responder})]_{\text{EUFLEXXA}} > [\text{probability}(\text{responder}) / \text{probability}(\text{non-responder})]_{\text{saline}}$

In the analysis of the secondary efficacy variable of OARSI responder rate using Wald chi-square test in the ITT population, the EUFLEXXA<sup>®</sup> group had a significantly larger responder rate than the saline

group at Week 26 for both response based on the 50-foot walk test (66.5% versus 58.7%; odds ratio 1.4; p-value = 0.047) and response based on WOMAC A (pain) scores (61.3% versus 51.9%; odds ratio 1.5; p-value = 0.028).

Other secondary analyses were done using repeated measure mixed model Analysis of Covariance (ANCOVA) from baseline through 26 weeks on mean change from baseline 50-foot walk test, measured on a 100mm horizontal VAS score improvement at 26 weeks, with a weekly injection of EUFLEXXA for 3 weeks.

At Week 26, the EUFLEXXA group of the ITT population showed a significantly larger decrease in WOMAC C (disability) scores from baseline than the placebo group (the change from baseline at 26 week for saline=-14.6, and for EUFLEXXA =-19.5, the difference from the baseline =-4.3 mm; p-value =0.019).

No significant group differences were observed for change in WOMAC A (pain, the change from baseline at 26 week for saline =-16.3, and for EUFLEXXA=-19.2, difference = -3.7, p=0.085) and B (joint stiffness, the change from baseline at 26 week for saline =-15.4, and for EUFLEXXA=-19.6, the difference from the baseline =-3.8, p=0.075) scores from baseline to Week 26.

In the analyses of Patient Global Assessment in the ITT population, the decrease in scores from baseline to Week 26 was significantly larger in the EUFLEXXA group than the placebo group (the change from baseline at 26 week for saline =-17.8 , and for EUFLEXXA =-22, the difference from the baseline = -4.5 mm; p-value = 0.035).

In the analysis of SF-36 Health Survey scores (physical component summary), the group difference in the least squares mean change in physical component summary scores from baseline was significant in favor of EUFLEXXA at 26 weeks (the baseline score for Placebo saline= 35.51, and for EUFLEXXA = 34.84, the difference from the baseline = 1.69 p-value = 0.021). The change in general health scores showed not a significance (p-value =0.055).

No significant treatment group differences were observed in the change in number of study-specific in the change in number of study specific acetaminophen tablets used per week or in the proportion of subjects who were pain free at week 26 and the end of the study.

**Table 9. Other Secondary Endpoints at 26 Weeks for ITT (n=291)**

	Change from Baseline at Week 26		The Least Square Mean difference in changes (EUFLEXXA - Saline) from the baseline <sup>b</sup>	2-sided test p-value <sup>a</sup>
	Saline (SD) (n=295)	EUFLEXXA (SD) (n=291)		
WOMAC <sup>c</sup> C (disability)	-14.6(25.79)	-19.5(24.68)	-4.3 mm	0.019
WOMAC B (joint stiffness)	-15.4 (29.33)	-19.6 (31.27)	-3.8	0.075
WOMAC A (pain)	-16.3 (26.82)	-19.2(26.81)	-3.3	0.085
Patient Global Assessment	-17.8(28.82)	-22(30.38)	-4.5	0.035

Note: The analysis is based on repeated measure mixed model Analysis of Covariance (ANCOVA) from baseline through 26 weeks on mean change from baseline.

<sup>a</sup> P-values are not adjusted for the multiplicity.

<sup>b</sup> Negative (-) values for WOMAC C and Patient Global Assessment are in favor of EUFLEXXA.

<sup>c</sup> The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a set of standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip. WOMAC Pain Scale is 100mm.

### **3. Efficacy Results of the Extension Phase Study after the Initial 26 weeks:**

The extension study was designed not to assess the effectiveness, but to provide the safety profile during the extension study, as the extension phase study was not either randomized or blinded.

## **XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION**

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices advisory panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

### **B. Panel Meeting Recommendation**

This PMA was not presented to the Orthopedic and Rehabilitation advisory panel, as the device is not the first of a kind and did not raise new question or issues needing panel input.

### **C. FDA's Post-Panel Action**

This PMA was not presented to the Orthopedic and Rehabilitation advisory panel, as the device is not the first of a kind.

## **XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Safety Conclusions**

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The submitted data provided a reasonable assurance that the device is safe for use in the reduction of pain in the osteoarthritis of the knee up to 26 weeks. The specific conclusions are:

During the initial randomization/treatment phase, 326 (55.4%) subjects in the safety population experienced 742 TEAEs.

- The proportion of subjects reporting TEAEs was generally similar in the EUFLEXXA<sup>®</sup> and saline groups (53.6% and 57.3%, respectively). The most common preferred term of TEAE was arthralgia (10.5% of all subjects). Thirty (5.1%) subjects experienced severe TEAEs, and the proportion with severe events was larger in the saline group (6.4%) than the EUFLEXXA<sup>®</sup> group (3.8%). Overall, 10.4% of subjects had TEAEs considered related to study device, with comparable proportions in each treatment group (9.9% and 10.8% for EUFLEXXA<sup>®</sup> and saline, respectively).
- During the extension phase, 43.4% (188/433) of subjects reported 377 TEAEs. Of these 43.8% (96/219) subjects receiving repeated EUFLEXXA<sup>®</sup> reported 199 TEAEs. The most frequently reported preferred term in subjects formerly assigned to the core study EUFLEXXA<sup>®</sup> group were arthralgia (8.7%), nasopharyngitis (4.6%), injury (4.1%), upper respiratory tract infections (2.7%), joint swelling (2.7%), back pain (2.7%), and sinusitis (2.3%). Of these TEAEs 9 (4.1%) subjects had study drug related AEs classified as "Certain," "Probable," "Possible" or "Un-

assessable.” The most common related TEAEs were arthralgia (2.3%) an joint swelling (1.4%). Table 2 show the Study Drug Related Treatment-Emergent Adverse Events by Preferred Term with an Incidence of > 1 among Treatment Groups (Safety Population).

### **B. Effectiveness Conclusions**

For the primary efficacy analysis, the analysis is based on repeated measure of mixed model of Analysis of Covariance (ANCOVA) from baseline through 26 weeks on mean change from baseline 50-foot walk test, measured on a 100mm horizontal VAS score improvement at 26 weeks, with a weekly injection of Euflexxa for 3 weeks. The submitted data provided a reasonable assurance that the device is effective for use in the reduction of pain in the osteoarthritis of the knee up to 26 weeks. The specific conclusions are:

- The analysis showed that the EUFLEXXA<sup>®</sup> group showed a larger mean (SD) decrease in pain scores on the 50-foot walk test from baseline to Week 26 than the saline group: - 25.7 (28.85) mm versus -18.5 (32.53) mm, respectively. The group difference in least squares mean change from baseline of -6.6 mm (95% CI = -10.8 to -2.5 mm) was statistically significant (p-value = 0.002).
- In the analysis of the secondary efficacy variable of OARSI responder rate using Wald chi-square test in the ITT population, the EUFLEXXA<sup>®</sup> group had a significantly larger responder rate than the saline group at Week 26 for both response based on the 50-foot walk test (66.5% versus 58.7%; odds ratio 1.4; p-value = 0.047) and response based on WOMAC A (pain) scores (61.3% versus 51.9%; odds ratio 1.5; p-value = 0.028).
- At Week 26, the EUFLEXXA group of the ITT population showed a significantly larger decrease in WOMAC C (disability) scores from baseline than the placebo group (the change from baseline at 26 week for saline=-14.6, and for EUFLEXXA =-19.5, the difference from the baseline = -4.3 mm; p-value =0.019).
- No significant group differences were observed for change in WOMAC A (pain, the change from baseline at 26 week for saline =-16.3, and for EUFLEXXA=-19.2, difference = -3.7, p=0.085) and B (joint stiffness, the change from baseline at 26 week for saline =-15.4, and for EUFLEXXA=-19.6, the difference from the baseline =-3.8, p=0.075) scores from baseline to Week 26.
- In the analyses of Patient Global Assessment in the ITT population, the decrease in scores from baseline to Week 26 was significantly larger in the EUFLEXXA group than the placebo group (the change from baseline at 26 week for saline =-17.8, and for EUFLEXXA =-22, the difference from the baseline = -4.5 mm; p-value = 0.035).
- In the analysis of SF-36 Health Survey scores (physical component summary), the group difference in the least squares mean change in physical component summary scores from baseline was significant in favor of EUFLEXXA at 26 weeks (the baseline score for Placebo saline= 35.51, and for EUFLEXXA = 34.84, the difference (Euflexxa- saline) from the baseline = 1.69 p-value = 0.021). The change in general health scores showed not a significance (p-value=0.055). No significant group differences were observed for other SF-36 scales, including physical function and bodily pain.

No significant treatment group differences were observed in the change in number of study-specific in the change in number of study specific acetaminophen tablets used per week or in the proportion of subjects who were pain free at week 26 or at the last visit.

Please note that the p-values of secondary endpoints were not adjusted for the multiplicity.

**C. Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the instruction for use.

**XIII. CDRH DECISION**

CDRH issued an approval order on October 11, 2011.

The applicant's manufacturing facility was not needed to be inspected as the already approved device (P010029) was used and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

**XIV. 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 are not required: See approval order.