SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Sodium Hyaluronate

Device Trade Name: SYNOJOYNT™

Device Procode: MOZ

Applicant's Name and Address: Teva Pharmaceuticals USA, Inc.
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170016

Date of FDA Notice of Approval: May 08, 2018

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the labeling for SYNOJOYNT™.

V. DEVICE DESCRIPTION

SYNOJOYNT™ is a sterile, non-pyrogenic, clear, viscoelastic solution of hyaluronan contained in a single-use prefilled syringe. SYNOJOYNT™ is a viscous solution of sodium hyaluronate in buffered physiological sodium chloride. The sodium hyaluronate is a high molecular weight fraction (approximately 2.5x106 daltons) of a natural complex sugar polymer consisting of repeating disaccharide units of Na-glucuronate-N acetylglucosamine. Two mL of SYNOJOYNT™ is supplied sterile, ready for injection,

in a 3 mL prefilled syringe packaged in a blister pack. The individual constituents of SYNOJOYNT™ are as follows:

Table 1: Constituents of SYNOJOYNT™

Component	Each Prefilled Syringe contains
Sodium Hyaluronate	20 mg
Sodium chloride	17 mg
Disodium hydrogen phosphate, heptahydrate	0.8 mg
Sodium dihydrogen phosphate, monohydrate	0.06 mg
Water for injection	q.s.* to 2.0 mL

*q.s. = up to

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the for the treatment of pain in osteoarthritis of the knee. The medical management of pain in osteoarthritis of the knee will depend on the severity of the condition and generally follows a progression from non-pharmacological management, through pharmacological management and intra-articular treatments to surgical options (Table 2).

Table 2: Treatment Options for Pain Due to Osteoarthritis of the Knee

Non-Pharmacological Treatments	Pharmacological Treatments	Intra-articular Treatments	Surgical Treatments
• Education • Social Support • Physical / Occupational Therapy • Weight Loss • Exercise • Orthotic devices • Transcutaneous electrical nerve stimulation (TENS) • Acupuncture	• Herbal remedies • Chondroitin and Glucosamine • Acetaminophen • NSAIDS • COX-2 Inhibitors • Topical NSAIDS • Topical Capsaicin • Opioid analgesics	• Corticosteroids • Hyaluronans • Tidal Irrigation	• Arthroscopy • Knee Replacement

Non-pharmacological management spans a wide range of approaches. Since obesity is a risk factor for osteoarthritis, overweight patients are counseled to lose weight and increase physical activity. Increased muscle strength may reduce certain osteoarthritis complications, so physical or occupational therapy may be recommended. The physical therapist may be able to direct patients to lower impact activities with less chance of exacerbating their osteoarthritis. Orthotic devices may provide some relief by minimizing load stresses. Transcutaneous electrical nerve stimulation and acupuncture may also provide temporary pain relief.

Pharmacological treatments are directed at either supplementing the lubrication functions of the joint (chondroitin and glucosamine) or pain management. Pain management

options range from acetaminophen and common non-steroidal anti- inflammatory drugs (NSAIDs), topical pain medications (NSAIDs and capsaicin), to COX-2 inhibitors.

Intra-articular treatments with either corticosteroids to reduce inflammation, or hyaluronates to provide additional lubrication may provide pain relief for several weeks. Intra-articular treatments may provide sufficient short term relief so as to delay surgical options.

Surgical options include both arthroscopy and partial or total knee replacement. Surgical options are generally reserved for those individuals who have failed all other treatment options.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

SYNOJOYNT™, manufactured by Hanmi Pharm. Co., Ltd., has been commercially marketed since 2009. The device received KFDA approval for marketing in Korea in 2009 and was CE Marked in the European Union in 2011. SYNOJOYNT™ has not been the subject of any recalls in any jurisdiction. SYNOJOYNT™ has not been withdrawn for any reason from any marketing jurisdiction.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g., complications) associated with the use of SYNOJOYNT™ are those that may occur in association with intra-articular injections. These include:

- arthralgia
- joint stiffness
- joint effusion
- joint swelling
- joint warmth
- injection site pain
- arthritis
- allergic reactions
- bleeding at the injection site
- potential infection

Post-market experience is available in Korea since 2009 and Europe since 2011. No reports of serious adverse events have been recorded for the SYNOJOYNT™ in those jurisdictions. For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Preclinical testing of SYNOJOYNT™ consisted of biocompatibility testing, leachables and extractables testing, and product stability testing.

Biocompatibility testing was conducted in accordance with ISO-10993-1:2009, *Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing within a Risk Management Process*. All testing was conducted on finished product consisting of 2 ml of 1% sodium hyaluronate in the 3 ml syringe. Test articles and controls were prepared in accordance with ISO 10993-12:2007, *Biological Evaluation of Medical Devices, Part 12: Sample Preparation and Reference Materials*. Testing was performed in compliance with Good Laboratory Practices (GLPs).

Cytotoxicity:
MEM extracts of SYNOJOYNT™ were incubated with cultured L-929 cells for 24 hours to evaluate cytotoxicity in accordance with ISO 10993-5. The cell monolayers were examined and scored based on the degree of cellular destruction. All test method acceptance criteria were met, confirming that SYNOJOYNT™ is non- cytotoxic.

Intracutaneous Irritation:
Saline and cottonseed oil extracts of SYNOJOYNT™ were tested for intracutaneous irritation by intracutaneous injection in albino rabbits (n=3), in accordance with ISO 10993-10. Each injection site was graded for tissue reaction (erythema and edema) at 24 ± 2, 48 ± 2 and 72 ± 2 hours after dose administration. The results showed no increase in irritation scores in the test as compared to control group, confirming that SYNOJOYNT™ is a non-irritant.

Sensitization:
Saline and cottonseed oil extracts of SYNOJOYNT™ were tested for the potential to produce a dermal sensitization reaction in a Guinea Pig Maximization Study, in accordance with ISO 10993-10. Thirty-four (34) guinea pigs (22 and 12 animals in the test and control groups, respectively) were used in this study. Animals were dosed with formulations of either test article or control article in three phases (2 inductions and 1 challenge). Dermal appearance of the dose sites was scored at 24 ± 2 h and 48 ± 2 h after challenge phase patch removal. The results demonstrated that the extracts did not cause sensitization reactions, confirming that SYNOJOYNT™ is non-sensitizing.

Genotoxicity (AMES):
DMSO (dimethyl sulfoxide) and saline extracts of SYNOJOYNT™ were tested for potential mutagenic activity in five Salmonella typhimurium strains (TA97, TA98, TA100, TA102 and TA1535) with and without activation, in accordance with ISO 10993-3. The test article extracts did not produce a two-fold or three-fold increase in the number of revertants in any of the 5 tester strains. The spot tests showed no zone of increased reversion or of toxicity. The results confirmed that SYNOJOYNT™ extracts tested against the five strains did not meet the criteria for a potential mutagen.

Genotoxicity (Mouse Micronucleus):
Saline and cottonseed oil extracts of SYNOJOYNT™ were evaluated for the potential to induce genotoxicity in a Mammalian Erythrocyte Micronucleus Genotoxicity Test, in accordance with ISO 10993-3. Forty-eight (24 male and 24 female) mice per test formulation were used (a total of 96 mice including controls). Half of each group of mice

were euthanized at 48 and at 72 hours post dose administration. Peripheral blood samples collected from 5 male and female mice of each group at each time point were processed for the flow cytometer analysis in accordance with the instructions for use of the Microflow micronucleus analysis kit (Litron Laboratories, Rochester, NY). The results showed no significant increase in micronucleated cells in any of the test article extracts as compared to negative controls, confirming that SYNOJOYNT™ is not genotoxic.

Genotoxicity (CHO Chromosome Aberration):
Extracts of SYNOJOYNT™ were evaluated for the potential to cause structural chromosome aberrations in Chinese Hamster Ovary (CHO) cells, in accordance with ISO 10993-3. The polar (F12KM) and DMSO extracts were placed on cells with and without metabolic activation. Stained chromosomes were examined for presence of aberrations. Positive control and test articles were compared to negative controls. The results showed no increase in chromosomal aberrations of the test article, confirming that SYNOJOYNT™ is not genotoxic.

Acute System Toxicity:
Saline and cottonseed oil extracts of SYNOJOYNT™ were evaluated for the systemic toxicity of leachable compounds by intraperitoneal injection into albino mice, in accordance with ISO 10993-11. Clinical observations were performed at pre-dose, immediately following dosing, at 4 (± 1) hours after dose administration, and thereafter daily for a period of at least 3 days. The results did not show a significantly greater biological reaction for the test article than the control article extracts, confirming that SYNOJOYNT™ did not cause systemic toxicity.

Intramuscular Implantation:
SYNOJOYNT™ was evaluated for the potential to cause a local tissue reaction by intramuscular implantation in the rabbit, in accordance with ISO 10993-6. Three animals were implanted with the test and control article. At necropsy, the implant and implant sites were collected, grossly evaluated for irritation and submitted for histopathology. The results indicated the test article did not cause local tissue irritation and therefore SYNOJOYNT™ is considered a non-irritant.

Hemocompatibility:
SYNOJOYNT™ was evaluated for the potential to cause hemolysis using the ASTM Hemolysis (Extract Method), in accordance with ISO 10993-4. Testing was performed in triplicate along with concurrent negative and positive controls. The results showed no hemolysis induced by the test article, indicating that SYNOJOYNT™ is non-hemolytic.

Pyrogenicity:
SYNOJOYNT™ was evaluated for the potential to produce a febrile response when injected intravenously in rabbits, in accordance with ISO 10993-11. Three New Zealand White rabbits received intravenous injections of a saline extract of the SYNOJOYNT™ test article. The results showed no significant increase in body temperature of the animals injected with the test article as compared to negative controls, indicating that SYNOJOYNT™ is non-pyrogenic.

Bacterial Endotoxins:
Limulus Ameobocyte Lysate (LAL) testing was performed on SYNOJOYNT™ to detect and quantify bacterial endotoxins using a kinetic turbidimetric methodology. The testing was conducted in accordance with USP <85>, EP 2.6.14 and JP 4.01. Test results showed an endotoxin level of <0.500 EU/ml, with a PPC recovery of 102%. The results confirm that the endotoxin level in SYNOJOYNT™ is below the established limit of 0.500 endotoxin units (EU)/ml.

Subchronic Toxicity:
SYNOJOYNT™ was evaluated for the potential to produce systemic toxicity and local irritation following three weekly consecutive subcutaneous injections to Yucatan minipigs, in accordance with ISO 10993-11 and ISO 10993-6. Following injection, animals were monitored with daily clinical observations and weekly body weights. Four animals per sex were sacrificed at 90 days. At necropsy, gross observations were made and tissues harvested, with tissues preserved and processed for histopathology. No treatment related adverse effects were observed in clinical signs, body weights, macroscopic necropsy observations, organ weights, hematology, clinical chemistry values, or in the microscopic evaluation of tissue slides of the test article. The results confirmed that SYNOJOYNT™ did not cause systemic toxicity or local tissue reaction.

Extractables/Leachables Testing:
Extractables and leachables testing was performed to evaluate the amounts of chemical substances present in the SYNOJOYNT™ gel and syringe delivery system. Testing was performed in accordance with ISO 10993-18, Biological Evaluation of Medical Devices – Part 18: Chemical Characterization of Materials. The results confirmed that there is no toxicological risk to the patient from extractables and leachables from the use of SYNOJOYNT™.

Glide Force Testing:
Glide force testing was performed to determine the extrusion force required to expel SYNOJOYNT™ from the pre-filled syringe. Testing confirmed that the design input requirement was met withthe use of either 19 or 21 gauge needles.

Product Stability Testing:
Stability testing was performed to support a 2 year shelf life for SYNOJOYNT™ at the recommended storage conditions of 2-25 °C.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of intra-articular (IA) injection into the knee with SYNOJOYNT™ 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). in the US under IDE # G150031. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The clinical study was a double-blinded, prospective, multi-site, randomized, three-arm, parallel group, pivotal investigation in adult subjects to evaluate the superiority of 3 weekly IA doses of 2 mL of SYNOJOYNT™ as compared to a placebo control (saline) injected into the target knee for the treatment of pain in subjects with OA. A total of 599 patients were treated and followed at 33 US sites between August 17, 2015, and December 5, 2016. The safety and effectiveness of SYNOJOYNT™ was also compared with EUFLEXXA®, another viscosupplement device approved under P010029.

The study was conducted as an adaptive investigation with two interim analyses (after approximately 50% and 75% of the planned sample size), allowing for sample size reassessment as needed. The study was considered complete (primary endpoint completion) once all subjects had completed the Week 26 follow-up visit. The primary effectiveness endpoint was the change from baseline in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score in the target knee at Week 26. The primary effectiveness endpoint was assessed for superiority of subjects treated with SYNOJOYNT™ in comparison to subjects treated with the saline placebo control. The analysis was performed using a repeated measures, mixed model, with treatment group and visit as factors and baseline WOMAC pain score as a covariate, and the treatment by visit, treatment by baseline and visit by baseline interactions.

1. Clinical Inclusion and Exclusion Criteria

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

   (1) Male or female, ≥ 40 years of age
   (2) Chronic OA of target knee confirmed by American College of Rheumatology Criteria
   (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 > 50 mm recorded on a 100 mm Visual Analogue Scale (VAS) immediately following a 50-foot walk at the Screening and Enrollment Visit
   (4) Subject agreed to discontinue all pain medications for at least 7 days prior to the Screening and Enrollment Visit
   (5) A standing anteroposterior X-ray of the target knee confirmed Grade 2 or 3 OA of the target knee by the Kellgren and Lawrence Grading Scale and was obtained within 6 months prior to the Screening and Enrollment Visit
      – Subjects that had OA in the non-target (contralateral) knee could have been enrolled in the investigation providing the target knee was the more symptomatic knee and met the criteria listed above. Pain in the non-target knee was to be limited to VAS < 40 mm following the 50-foot walk test at Screening
   (6) Body mass index ≤ 40 kg/m^2

(7) Was able and willing to use only acetaminophen as the analgesic (rescue) investigational medication under the following conditions:
   - Acetaminophen dose was not to exceed 4 g (4000 mg) per day
   - If the subject had a known chronic liver disease, the maximum dose of acetaminophen was not to exceed 2 g (2000 mg) per day
   - Subject was able and willing o discontinue acetaminophen at least 24 hours prior to all investigation-specific visits
   - The provided investigation-specific acetaminophen was only to be used for knee pain
(8) Had the ability to perform the procedures required for the pain index evaluations
(9) Females who were of childbearing potential agreed to use a highly effective contraception from 2 weeks prior to administration of the first investigational device until investigation completion:
   - Hormonal contraception
   - Intra-uterine device (which should have been established prior to the start of the investigation)
   - Double barrier method (condom, sponge, diaphragm or vaginal ring with spermicidal jelly or cream)
   - Stable relationship with vasectomized partner
   - If practicing abstinence or in a same-sex relationship agreed to use an acceptable contraceptive method if the decision was made to become sexually active with a male partner
(10) Was able and willing to complete the effectiveness and safety questionnaires and able to read and understand investigation instructions
(11) Signed the investigation-specific Informed Consent Form (ICF).

Patients were <u>not</u> permitted to enroll in the study if they met any of the following exclusion criteria:

(1) Had any major injury (including sports injuries) to the target knee within the 12 months prior to the Screening and Enrollment Visit
(2) Had received any HA injection into the arget knee within 6 months prior to first investigational treatment
(3) Had any surgery to the target knee within the 12 months prior to the Screening and Enrollment Visit, or surgery to the contralateral knee or other weight-bearing joint that would have interfered with knee assessments
(4) Had received articular procedures such as transplants or ligament reconstruction to the target knee within 12 months prior to Screening and Enrollment Visit
(5) Had inflammatory arthropathies such as rheumatoid arthritis, lupus arthropathy, or psoriatic arthritis
(6) Had gout or calcium pyrophosphate (pseudogout) diseases of the target knee that had flared within the 6 months prior to the Screening and Enrollment Visit

(7) Had X-ray findings of acute fractures, severe loss of bone density, avascular necrosis, and/or severe bone or joint deformity in the target knee
(8) Had osteonecrosis of either knee
(9) Had clinical signs and symptoms of an active knee infection or crystal disease of the target knee
(10) Had fibromyalgia, pes anserine bursitis, lumbar radiculopathy, and/or neurogenic or vascular claudication
(11) Had significant anterior knee pain due to diagnosed isolated patella-femoral syndrome or chondromalacia in the target knee
(12) Had significant target knee joint infection or skin disorder infection within the 6 months prior to study enrollment
(13) Had symptomatic osteoarthritis of the hips, spine, or ankle, that interferes with the evaluation of the target knee
(14) Had known hypersensitivity to acetaminophen or any of the study medications or their components
(15) Women of childbearing potential who are pregnant, nursing, or planning to become pregnant, or who do not agree to remain on an acceptable method of birth control throughout the entire study period
(16) Had a history of recurrent severe allergic or immune mediated reactions or other immune disorders
(17) Had vascular insufficiency of lower limbs or peripheral neuropathy severe enough to interfere with the study evaluation
(18) Had been injected with an intra-articular corticosteroid (investigational or marketed) in any joint within 3 months of Screening and Enrollment Visit
(19) Was undergoing current treatment, or treatment within the 2 years prior to the Screening and Enrollment Visit, for any malignancy, unless specific written permission was provided by the Sponsor (excluding basal cell or squamous cell carcinoma of the skin)
(20) Had active liver disease based on liver profile of aspartate aminotransferase, alanine aminotransferase, and conjugated bilirubin > 2 times the upper limit of normal
(21) Had renal insufficiency based on serum creatinine > 2.0 mg/dL
(22) Had any clinically significant laboratory value that the Investigator feels, based on clinical history, might affect the study evaluation
(23) Had any intercurrent chronic disease or condition that might interfere with the completion of the study, such as liver disease, severe coronary disease, drug abuse, disordered mental state, or other clinically significant condition
(24) Current alcoholism and/or any known current addiction to pain medications
(25) Had any clinically significant finding that placed the subject at health risk, impacted the study, or affected completion of the study
(26) Had any psychiatric illness that prevented comprehension of the details and nature of the study
(27) Had any other clinically significant acute or chronic medical conditions (e.g., bleeding disorder) that, in the judgment of the Investigator, would preclude the use of an IA injection or that could compromise subject safety,

limit the subject's ability to complete the study, and/or compromise the objectives of the study

(28) Participation in any experimental device study within 6 months prior to the Screening and Enrollment Visit, or participation in an experimental drug study within 1 month prior to the Screening and Enrollment Visit.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 3,6,12,18 and 26 weeks. The schedule of assessments is presented in Table 3. Adverse events and complications were recorded at all visits.

Table 3. Schedule of Assessments

Procedure/Assessment	**Screening and Enrollment**	**Treatment (±3 days)**			**Follow-Up (± 3 days)**				**EOS (±7 days)**	**Unscheduled Visit**
Day/Week	**Day -21 to Day -1**	**Day 1**	**Day 7 Week 1**	**Day 14 Week 2**	**Day 21 Week 3**	**Day 42 Week 6**	**Day 84 Week 12**	**Day 126 Week 18**	**Day 182 Week 26**	
Visit Number	1	2	3	4	5	6	7	8	9	
ICF	X									
Inclusion/Exclusion criteria	X									
Subject information/medical history	X									
Confirmation of eligibility		X								
Pregnancy[1]	X	X[3]							X	
Physical examination, vital signs	X[2]				X				X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X
SF-36[3]	X	X					X		X	
WOMAC[3]	X	X	X	X	X	X	X	X	X	X
Target knee assessment[4]	X	X	X	X	X	X	X	X	X	X
Distribution/return/tracking of rescue acetaminophen	X	X	X	X	X	X	X	X	X	
Hematology/Biochemistry	X									X
Target knee X-ray	X									
Randomization		X								
Investigational Device Administration [5, 6]		X	X	X						
Adverse events	X	X	X	X	X	X	X	X	X	X

EOS = End of Study; ICF = Informed Consent Form; SAE = serious adverse event; SF-36 = Short Form (36); VAS = Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index

1. Urine pregnancy test was in women of childbearing potential only. Urine pregnancy test at Visit 2/Day 1 only if Screening test was ≥ 14 days.
2. Height and weight was to be measured at the Screening Visit only.
3. Was to be conducted prior to knee aspiration (if required) and investigational device administration.
4. Target knee was to be assessed for tenderness, heat/redness, swelling, and effusion.
5. Aspiration of target knee was to be performed prior to treatment administration only if joint effusion was present.
6. All safety and effectiveness assessments were to be completed prior to treatment administration.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint for this investigation was the incidence of adverse events (AEs). Secondary safety endpoints included the following:

- Incidence of serious adverse events (SAEs)
- Laboratory values: hematology/biochemistry
- Vital signs
- Physical examination.

With regards to effectiveness, the primary effectiveness endpoint was the change from Baseline in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score in the target knee at Week 26. Secondary effectiveness endpoints included the following:

- The change from baseline in the WOMAC pain score over time
- Pain, stiffness and physical function of the target knee as assessed by WOMAC over time
- The change from baseline in the Short Form (36) (SF-36) over time.

With regard to success/failure criteria, it was hypothesized that SYNOJOYNT™ would demonstrate superiority with respect to a saline placebo control for a least square mean change from baseline in the WOMAC pain score in the target knee at Week 26 and that the incidence of AEs would be comparable in the SYNOJOYNT™ and saline placebo control treatment groups. However, quantified measures for individual patient success, as well as overall study success were not predefined in the protocol.

B. Accountability of PMA Cohort

At the time of database lock, of 599 patients enrolled in the PMA study, 543 (90.7%) patients were available for analysis at the completion of the study, the Week 26 (23 weeks post-treatment) visit. 1053 patients were initially screened for entry into the study. 178 of 200 patients (89.0%) enrolled in the SYNOJOYNT™ treatment arm were treated and completed the study; 184 of 200 patients (92.0%) enrolled in the EUFLEXXA® treatment arm were treated and completed the study; and 181 of 199 patients (91.0%) enrolled in the saline placebo control treatment arm were treated and completed the study.

All 599 enrolled patients were included in the intent-to treat (ITT population). In total, 545 (91.0%) patients and 595 (99.3%) patients were included in the PP population and Safety Analysis population, respectively. There were no deaths recorded as primary reason for discontinuation of study. Overall, the most common reason for discontinuation of study was subject withdrew consent (25 patients [4.2%]). Details are provided in the following Subject Disposition Table (Table 4).

Table 4: Subject Disposition - All Subjects

Number (%) of Subjects	Placebo n (%)	EUFLEXXA® n (%)	SYNOJOYNT™ n (%)	Total n (%)
Screened (N)				1053
Screen Failure (N)				454 (43.1)
Enrolled	199	200	200	599
Treated	197 (99.0)	199 (99.5)	199 (99.5)	595 (99.3)
Completed	181 (91.0)	184 (92.0)	178(89.0)	543 (90.7)
Discontinued	18 (9.0)	16 (8.0)	22 (11.0)	56 (9.3)
Analysis Population				
ITT Population	199 (100.0)	200 (100.0)	200 (100.0)	599 (100.0)
PP	183 (92.0)	180(90.0)	182 (91.0)	545 (91.0)
Safety Analysis Population	197 (99.0)	199 (99.5)	199 (99.5)	595 (99.3)
Primary Reason for Discontinuation of Study:				
Adverse Event	1 (0.5)	0	5 (2.5)	6 (1.0)
Subject Withdrew	10 (5.0)	6 (3.0)	9 (4.5)	25 (4.2)
Consent				
Investigators Decision	0	1 (0.5)	0	1 (0.2)
Protocol	2 (1.0)	1 (0.5)	1 (0.5)	4 (0.7)
Non-Compliance				
Lost to FU	3 (1.5)	5 (2.5)	4 (2.0)	12 (2.0)
Other	2(1.0)	3(1.5)	3(1.5)	8(1.3)

Note: Screen failure percentage was calculated from number of screened subjects and other percentages were calculated among number of enrolled subjects. A subject was considered enrolled once they had successfully completed their Screening assessments, had their eligibility re-confirmed on Day 1, and had been randomized to treatment. Enrolled was the same as ITT.
Abbreviations: FU=Follow-up; ITT=intention-to-treat; PP=per-protocol; N/n=number of subjects.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population were typical for a study of pain reduction of OA performed in the US. Demographic and baseline characteristics were generally similar across treatment groups. The majority of subjects in the study were White (484 [80.8%] subjects: 160 [80.4%] subjects placebo group, 161 [80.5%] subjects EUFLEXXA® group, 163 [81.5%] subjects SYNOJOYNT™ group) and not of Hispanic/Latino ethnicity (421 [70.3%] subjects: 145 [72.9%] subjects placebo group, 146 [73.0%] subjects EUFLEXXA® group, 130 [65.0%] subjects SYNOJOYNT™ group). More subjects were female (348 [58.1%] subjects: 110 [55.3%] subjects placebo group, 117 [58.5%] subjects EUFLEXXA® group, 121 [60.5%] subjects SYNOJOYNT™ group). The overall mean age was 62.8 years (range: 40.0 to 87.0 years).

Target knee was assessed for tenderness, swelling, redness/heat, effusion. Clinically significant target knee assessments at baseline (collected at screening visit, if not treated) were tenderness (15 [2.5%] subjects); swelling (6 [1.0%] subjects), effusion (3 [0.5%] subjects) and redness/heat (1 [0.2%] subject). At baseline, the target knee assessment for tenderness, swelling, redness/heat, or effusion was similar for each treatment group.

At baseline, all (except 1 subject who had a missing value) subjects had Kellgren-Lawrence Grade 2 (336 [56.1%] subjects) or Grade 3 (262 [43.7%] subjects) of OA (as identified by the target knee X-ray).

Detailed demographic data are provided below in Table 5.

Table 5. Demographic and Baseline Characteristics – ITT Population

Characteristic	Placebo N=199 n (%)	EUFLEXXA® N=200 n (%)	SYNOJOYNT™ N=200 n (%)	Total N=599 n (%)
Age (years)				
N	199	200	200	599
Mean	62.0	63.3	63.2	62.8
SD	10.04	9.36	9.45	9.62
Minimum	40	40	43	40
Median	62.0	63.0	63.0	63.0
Maximum	87	85	86	87
Sex				
Male	89 (44.7)	83 (41.5)	79 (39.5)	251 (41.9)
Female	110 (55.3)	117 (58.5)	121 (60.5)	348 (58.1)
Ethnicity				
Hispanic or Latino	54 (27.1)	54 (27.0)	70 (35.0)	178 (29.7)
Not Hispanic or Latino	145 (72.9)	146 (73.0)	130 (65.0)	421 (70.3)
Race				
American Indian or Alaska Native	0	2 (1.0)	1 (0.5)	3 (0.5)
Asian	8 (4.0)	10 (5.0)	13 (6.5)	31 (5.2)
Black or African	31 (15.6)	27 (13.5)	20 (10.0)	78 (13.0)
American				
Native Hawaiian or Other Pacific Islander	0	0	1 (0.5)	1 (0.2)
White	160 (80.4)	161 (80.5)	163 (81.5)	484 (80.8)
Multiple	0	0	1 (0.5)	1 (0.2)
Other	0	0	1 (0.5)	1 (0.2)
Height (cm)				
N	199	200	200	599
Mean	168.21	169.81	167.23	168.42
SD	11.578	22.651	10.073	15.812
Minimum	125.0	136.5	144.8	125.0
Median	167.64	167.64	167.00	167.64
Maximum	196.6	452.1	190.5	452.1
Weight (kg)				
N	199	200	200	599
Mean	87.67	84.76	84.54	85.65
SD	17.967	17.653	16.584	17.440
Minimum	45.9	49.1	50.9	45.9
Median	87.27	84.09	81.82	84.09
Maximum	141.4	140.9	130.1	141.4
Target Knee Assessment – Clinically Significant Finding				
Tenderness	6 (3.0)	4 (2.0)	5 (2.5)	15 (2.5)
Swelling	1 (0.5)	2 (1.0)	3 (1.5)	6 (1.0)
Redness/Heat	0	1 (0.5)	0	1(0.2)

Effusion	0	2 (1.0)	1 (0.5)	3 (0.5)
Kellgren-Lawrence Grade of Target Knee X-ray				
Grade 0	0	0	0	0
Grade 1	0	0	0	0
Grade 2	104 (52.3)	124 (62.0)	108 (54.0)	336 (56.1)
Grade 3	95 (47.7)	76 (38.0)	91 (45.5)	262 (43.7)
Grade 4	0	0	0	0
Missing	0	0	1 (0.5)	1 (0.2)

Abbreviations: ITT=intention-to-treat; n/N=number of subjects; SD=Standard Deviation

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Safety Analysis Population cohort of 595 treated patients. The adverse effects and key safety outcomes for this study are presented below in Tables 6 to 10.

Adverse effects that occurred in the PMA clinical study:

Overall, the incidence of Treatment-Emergent Adverse Events (TEAEs) in the SYNOJOYNT™ treatment group was similar to that of the saline placebo treatment group. In total, 234 (39.3%) subjects experienced 411 TEAEs: 147 TEAEs in the placebo group; 135 TEAEs in the EUFLEXXA® group; 129 TEAEs in the SYNOJOYNT™ group. In total, 9 (1.5%) subjects (3 [1.5%] subjects placebo group; 1[0.5%] subject EUFLEXXA® group; 5 [2.5%] subjects SYNOJOYNT™ group) had a treatment-emergent SAE.

There were 8 (1.3%) subjects with severe TEAEs in total. In all, there were 114 (19.2%) subjects with target knee-related TEAEs (45 [22.8%] subjects placebo group; 37 [18.6%] subjects EUFLEXXA® group; 32 [16.1%] subjects SYNOJOYNT™ group) and 31 (5.2%) subjects with any injection-related TEAEs (12 [6.1%] subjects placebo group; 9[4.5%] subject EUFLEXXA® group; 10[5.0%] subjects SYNOJOYNT™ group). There were no deaths or unexpected adverse device event (UADEs) in the study. Overall TEAEs are summarized below in Table 6.

Table 6: Overall Summary of TEAEs – Safety Analysis Population

	Placebo N=197 n (%)	EUFLEXXA® N=199 n (%)	SYNOJOYNT™ N=199 n (%)	Total N=595 n (%)
Number of TEAE(s)[1]	147	135	129	411
Subjects with Any TEAE(s)	76 (38.6)	82 (41.2)	76 (38.2)	234 (39.3)
Subjects with Any Serious Adverse Event	3 (1.5)	1 (0.5)	5 (2.5)	9 (1.5)
Subjects with Any Severe TEAE(s)	3 (1.5)	2 (1.0)	3 (1.5)	8 (1.3)
Subjects with Any Target Knee-Related TEAE(s)	45 (22.8)	37 (18.6)	32 (16.1)	114 (19.2)
Subjects with Any Device-Related TEAE(s)	11 (5.6)	10 (5.0)	7 (3.5)	28 (4.7)

Subjects with Any Injection-Related TEAE(s)	12 (6.1)	9 (4.5)	10 (5.0)	31 (5.2)
Subjects with Any Unanticipated Adverse Device Effect	0	0	0	0
Subjects with TEAE(s) Leading to Study Discontinuation	1 (0.5)	0	4 (2.0)	5 (0.8)
Subjects with TEAE(s) Leading to Death	0	0	0	0

Note: TEAEs were those AEs which worsened in severity on or after date of first administration of study device or with onset date on or after date of first administration of study device.

Except for the number of AEs, subjects were counted only once per treatment in each row.

MedDRA V18.1 coding dictionary was used.

Abbreviation: AE(s)=adverse event(s); MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of subjects; SAE=serious adverse event; TEAE(s)=treatment-emergent adverse events.

1. For each subject, multiple AEs sharing the same MedDRA preferred term were counted only once.

AEs which led to discontinuation are summarized by SOC (system organ class) and PT (Preferred Term) in Table 7 below.

Table 7: Discontinuations of Subjects Due to TEAEs by System Organ Class and Preferred Term - Safety Analysis Population

System Organ Class Preferred Term	Placebo N=197 n (%)	EUFLEXXA® N=199 n (%)	SYNOJOYNT™ N=199 n (%)	Total N=595 n (%)
Subjects who discontinued due to TEAEs	1 (0.5)	0	4 (2.0)	5 (0.8)
General disorders and administration site conditions	0	0	1 (0.5)	1 (0.2)
Injection site joint pain	0	0	1 (0.5)	1 (0.2)
Injury, poisoning and procedural complications	0	0	1 (0.5)	1 (0.2)
Wrist fracture	0	0	1 (0.5)	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.5)	0	2 (1.0)	3 (0.5)
Arthralgia	1 (0.5)	0	1 (0.5)	2 (0.3)
Haemarthrosis	1 (0.5)	0	0	1 (0.2)
Joint effusion	1 (0.5)	0	0	1 (0.2)
Joint swelling	1 (0.5)	0	0	1 (0.2)
Osteoarthritis	0	0	1 (0.5)	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.5)	0	0	1 (0.2)
Erythema	1 (0.5)	0	0	1 (0.2)

Note: TEAEs were those AEs which worsened in severity on or after date of first administration of study device or with onset date on or after date of first administration of study device.

MedDRA V18.1 coding dictionary was used.

Abbreviation: AE(s)=adverse event(s); MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of subjects; TEAE(s)=treatment-emergent adverse events.

In all, 5 (0.8%) subjects had a TEAE leading to study discontinuation (1 [0.5%] subject placebo group; 4 [2.0%] subjects SYNOJOYNT™ group). No subject in the EUFLEXXA® group had a TEAE leading to study discontinuation.

A summary of TEAEs by SOC and PT is provided in and summarized by SOC below in Table 8. In total, 234 (39.3%) subjects experienced 411 TEAEs: 147 TEAEs placebo group; 135 TEAEs EUFLEXXA® group; 129 TEAEs SYNOJOYNT™ group (Table 6). Overall, the number of subjects with TEAEs in the SYNOJOYNT™ group (38.2%) was comparable with that of the placebo group (38.6%).

Table 8. Summary of TEAEs by SOC– Safety Analysis Population

System Organ Class Preferred Term	Placebo N=197 n (%)	EUFLEXXA® N=199 n (%)	SYNOJOYNT™ N=199 n (%)	Total N=595 n (%)
Subjects with Any TEAE(s)	76 (38.6)	82 (41.2)	76 (38.2)	234 (39.3)
Blood and lymphatic system disorders	0	1 (0.5)	0	1 (0.2)
Cardiac disorders	0	1 (0.5)	1 (0.5)	2 (0.3)
Ear and labyrinth disorders	2 (1.0)	0	1 (0.5)	3 (0.5)
Eye disorders	0	3 (1.5)	2 (1.0)	5 (0.8)
Gastrointestinal disorders	5 (2.5)	7 (3.5)	5 (2.5)	17 (2.9)
General disorders and administration site conditions	20 (10.2)	13 (6.5)	13 (6.5)	46 (7.7)
Hepatobiliary disorders	1 (0.5)	1 (0.5)	0	2 (0.3)
Immune system disorders	2 (1.0)	0	0	2 (0.3)
Infections and infestations	18 (9.1)	26 (13.1)	23 (11.6)	67 (11.3)
Injury, poisoning and procedural complications	6 (3.0)	7 (3.5)	5 (2.5)	18 (3.0)
Investigations	1 (0.5)	3 (1.5)	1 (0.5)	5 (0.8)
Metabolism and nutrition disorders	1 (0.5)	1 (0.5)	2 (1.0)	4 (0.7)
Musculoskeletal and connective tissue disorders	32 (16.2)	34 (17.1)	30 (15.1)	96 (16.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.5)	2 (1.0)	2 (1.0)	7 (1.2)
Nervous system disorders	9 (4.6)	4 (2.0)	10 (5.0)	23 (3.9)
Psychiatric disorders	3 (1.5)	0	0	3 (0.5)
Renal and urinary disorders	2 (1.0)	0	1 (0.5)	3 (0.5)
Respiratory, thoracic and mediastinal disorders	3 (1.5)	4 (2.0)	7 (3.5)	14 (2.4)

Skin and subcutaneous tissue disorders	3 (1.5)	1 (0.5)	0	4 (0.7)
Vasculardisorders	0	0	1 (0.5)	1 (0.2)

Overall, the most frequently experienced TEAEs (all causalities) by SOC for the Safety Analysis Set were:

- Musculoskeletal and connective tissue disorders: the three most common TEAEs (all causalities) by PT were:
  - Arthralgia: 69 (11.6%) subjects (24 [12.2%] subjects placebo group; 26 [13.1%] subject EUFLEXXA® group; 19 [9.5%] subjects SYNOJOYNT™ group)
  - Joint swelling: 15 (2.5%) subjects (7 [3.6%] subjects placebo group; 3 [1.5%] subject EUFLEXXA® group; 5 [2.5%] subjects SYNOJOYNT™ group)
  - Joint crepitation: 12 (2.0%) subjects (4 [2.0%] subjects placebo group; 3 [1.5%] subject EUFLEXXA® group; 5 [2.5%] subjects SYNOJOYNT™ group)
- Infections and infestations: the three most common TEAEs (all causalities) by PT were:
  - Upper respiratory tract infection: 17 (2.9%) subjects (3 [1.5%] subjects placebo group; 7 [3.5%] subject EUFLEXXA® group; 7 [3.5%] subjects SYNOJOYNT™ group)
  - Nasopharyngitis: 16 (2.7%) subjects (8 [4.1%] subjects placebo group; 3 [1.5%] subject EUFLEXXA® group; 5 [2.5%] subjects SYNOJOYNT™ group)
  - Bronchitis: 6 (1.0%): (0 subjects placebo group; 1 [0.5%] subject EUFLEXXA® group; 5 [2.5%] subjects SYNOJOYNT™ group) and Urinary tract infection: 6 (1.0%): 2 (1.0%) in each treatment group
- General disorders and administration site conditions: the three most common TEAEs (all causalities) by PT were:
  - Injection site joint pain: 18 (3.0%) (12 [6.1%] subjects placebo group; 1 [0.5%] subject EUFLEXXA® group; 5 [2.5%] subjects SYNOJOYNT™ group)
  - Injection site joint effusion: 8 (1.3%) (3 [1.5%] subjects placebo group; 4 [2.0%] subject EUFLEXXA® group; 1 [0.5%] subjects SYNOJOYNT™ group)
  - Injection site joint swelling: 6 (1.0%) (3 [1.5%] subjects placebo group; 2 [1.0%] subject EUFLEXXA® group; 1 [0.5%] subjects SYNOJOYNT™ group)

Overall, in the SYNOJOYNT™ group the incidence of target knee-related TEAEs was comparable with that of the placebo group (32 [16.1%] subjects in the SYNOJOYNT™ group versus 45 [22.8%] subjects in the placebo group).

Target knee-related TEAEs were most commonly associated with the musculoskeletal and connective tissue disorders SOC (26 [13.2%] subjects in the placebo group, 27 [13.6%] subjects in the EUFLEXXA® group, 23 [11.6%] subjects in the SYNOJOYNT™ group) and the general disorders and administration site conditions SOC (18 [9.1%] subjects in the placebo group, 10 [5.0%] subjects in the EUFLEXXA® group, 9 [4.5%] subjects in the SYNOJOYNT™ group).

The three most common target knee-related TEAEs, by PT were arthralgia (21 [10.7%] subjects in the placebo group, 24 [12.1%] subjects in the EUFLEXXA® group, 17 [8.5%] subjects in the SYNOJOYNT™ group), injection site joint pain (12 [6.1%] subjects in the placebo group, 1 [0.5%] subjects in the EUFLEXXA® group, 5 [2.5%] subjects in the SYNOJOYNT™ group) and joint swelling (6 [3.0%] subjects in the placebo group, 2 [1.0%] subjects in the EUFLEXXA® group, 5 [2.5%] subjects in the SYNOJOYNT™ group).

Target knee-related TEAEs are summarized by SOC and PT in Table 9 below.

Table 9: Summary of Target Knee-Related TEAEs by SOC and PT– Safety Analysis Population

System Organ Class Preferred Term	Placebo N=197 n (%)	EUFLEXXA® N=199 n (%)	SYNOJOYNT™ N=199 n (%)
Subjects with any Target Knee-Related TEAEs	45 (22.8)	37 (18.6)	32 (16.1)
General disorders and administration site conditions	18 (9.1)	10 (5.0)	9 (4.5)
Injection site bruising	1 (0.5)	0	0
Injection site erythema	0	2 (1.0)	0
Injection site haemorrhage	1 (0.5)	0	0
Injection site joint effusion	3 (1.5)	4 (2.0)	1 (0.5)
Injection site joint pain	12 (6.1)	1 (0.5)	5 (2.5)
Injection site joint swelling	3 (1.5)	2 (1.0)	1 (0.5)
Injection site joint warmth	0	2 (1.0)	0
Injection site pain	1 (0.5)	2 (1.0)	2 (1.0)
Injection site reaction	1 (0.5)	0	0
Injection site swelling	1 (0.5)	0	0
Mass	0	1 (0.5)	0
Swelling	0	0	1 (0.5)
Tenderness	0	0	1 (0.5)
Infections and infestations			
Injection site infection	0	1 (0.5)	0
Injury, poisoning and procedural complications	4 (2.0)	2 (1.0)	1 (0.5)
Contusion	1 (0.5)	0	0
Laceration	0	0	1 (0.5)

Meniscus injury	0	1 (0.5)	0
Muscle rupture	1 (0.5)	0	0
Procedural pain	0	1 (0.5)	0
Skin abrasion	1 (0.5)	1 (0.5)	0
Soft tissue injury	1 (0.5)	0	0
Musculoskeletal and connective tissue disorders	26 (13.2)	27 (13.6)	23 (11.6)
Arthralgia	21 (10.7)	24 (12.1)	17 (8.5)
Exostosis	0	2 (1.0)	0
Haemarthrosis	1 (0.5)	0	0
Joint crepitation	4 (2.0)	3 (1.5)	4 (2.0)
Joint effusion	4 (2.0)	2 (1.0)	4 (2.0)
Joint range of motion decreased	1 (0.5)	1 (0.5)	0
Joint stiffness	1 (0.5)	0	1 (0.5)
Joint swelling	6 (3.0)	2 (1.0)	5 (2.5)
Joint warmth	1 (0.5)	0	0
Osteoarthritis	0	1 (0.5)	1 (0.5)
Tendonitis	1 (0.5)	0	0
Nervous system disorders	2 (1.0)	0	0
Paraesthesia	1 (0.5)	0	0
Presyncope	1 (0.5)	0	0
Psychiatric disorders	1 (0.5)	0	0
Depression	1 (0.5)	0	0
Skin and subcutaneous tissue disorders	2 (1.0)	0	0
Erythema	2 (1.0)	0	0

Overall, in the SYNOJOYNT™ group the incidence of device-related TEAEs was low and comparable with the placebo group (7 [3.5%] subjects in the SYNOJOYNT™ group versus 11 [5.6%] subjects in the placebo group).

The three most common device-related TEAEs, by PT were injection site joint pain (5 [2.5%] subjects in the placebo group, 1 [0.5%] subjects in the EUFLEXXA® group, 2 [1.0%] subjects in the SYNOJOYNT™ group), arthralgia (2 [1.0%] subjects in the placebo group, 4 [2.0%] subjects in the EUFLEXXA® group, 2 [1.0%] subjects in the SYNOJOYNT™ group) and injection site joint effusion (2 [1.0%] subjects in the placebo group, 1 [0.5%] subjects in the EUFLEXXA® group, 1 [0.5%] subjects in the SYNOJOYNT™ group).

Device-related TEAEs by SOC and PT are summarized below in Table 10.

Table 10: Summary of Device-Related TEAEs by SOC and PT – Safety Analysis Population

System Organ Class Preferred Term	Placebo N=197 n(%)	EUFLEXXA® N=197 n(%)	SYNOJOYNT™ N=199 n(%)
Subjects with any Device-related TEAEs	11 (5.6)	10(5.0)	7 (3.5)
General disorders and administration site conditions	8 (4.1)	5 (2.5)	4 (2.0)
Injection site erythema	0	1(0.5)	0

Injection site joint effusion	2 (1.0)	1(0.5)	1 (0.5)
Injection site joint pain	5 (2.5)	1(0.5)	2 (1.0)
Injection site joint swelling	0	2(1.0)	1 (0.5)
Injection site joint warmth	0	1(0.5)	0
Injection site pain	0	1(0.5)	1 (0.5)
Injection site reaction	1 (0.5)	0	0
Infections and infestations	0	1(0.5)	0
Injection site infection	0	1(0.5)	0
Musculoskeletal and connective tissue disorders	2 (1.0)	4(2.0)	3 (1.5)
Arthralgia	2 (1.0)	4(2.0)	2 (1.0)
Haemarthrosis	1 (0.5)	0	0
Joint effusion	1 (0.5)	0	0
Joint stiffness	1 (0.5)	0	1 (0.5)
Joint swelling	1 (0.5)	1(0.5)	0
Nervous system disorders	1 (0.5)	0	0
Presyncope	1 (0.5)	0	0
Skin and subcutaneous tissue disorders	1 (0.5)	0	0
Erythema	1 (0.5)	0	0

Note: TEAEs were those AEs which worsened in severity on or after date of first administration of study device or with onset date on or after date of first administration of study device.

MedDRA V18.1 coding dictionary was used.

Abbreviation: AE(s)=adverse event(s); MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of subjects; TEAE(s)=treatment-emergent adverse events.

Potential adverse effects (e.g., complications) associated with the use of this device and, in general, associated with intra-articular injection devices for the treatment of pain in osteoarthritis of the knee, include:

- Aggravated osteoarthritis
- Injection site reaction
- Arthralgia (knee pain)
- Localized osteoarthritis
- Arthropathy
- Joint (knee) disorder
- Arthrosis
- Joint (knee) swelling
- Baker's cyst
- Joint (knee) effusion
- Bursitis
- Joint (knee) stiffness
- Immune response
- Pain in limb
- Infection
- Paraesthesia
- Injection site erythema
- Phlebitis

- Injection site edema
- Pruritis
- Injection site pain
- Tendonitis

Incidences of rash, headache, dizziness, chills, hives, nausea, muscle cramps, peripheral edema, and malaise have also been reported in association with intra-articular injections.

2. Effectiveness Results

The analysis of effectiveness was based on the mean change from baseline in the WOMAC pain score in the target knee at Week 26 for 399 ITT population patients (200 SYNOJOYNT™ patients and 199 placebo control patients). Key effectiveness outcomes are presented in Tables 11 and 12 and Figure 1.

From a statistical perspective, the data from the clinical study demonstrated the superiority of the test device over placebo in the reduction of mean WOMAC pain score at Week 26. As one third (1/3) of the study sites showed smaller reduction in the test group compared to the placebo group, there were issues of poolability between sites, and the change in WOMAC pain scores at week 26, the primary effectiveness endpoint, was reanalyzed with the final data using a mixed model with repeated measures. The model included baseline assessment as a covariate and fixed effects of treatment, visit, treatment-by-visit, site and site-by-treatment interaction. A Type 3 test for fixed effect of site-by-treatment interaction had a p-value equal to 0.0580. Treatment effect was assessed within each site for a p-value of < 0.15. The estimated treatment effect size and its standard error with each site showed that there was no specific pattern observed across sites, indicating that the data can be pooled from each site.

At the Week 26 visit the least squares (LS) mean change (± SD) from baseline in WOMAC pain scores was -131.64 (9.35) in the placebo group versus -167.73 (9.32) in the SYNOJOYNT™ group. At the Week 26 visit the difference (placebo versus SYNOJOYNT™) in mean change from baseline in WOMAC pain score was significantly greater for the SYNOJOYNT™ group versus the placebo group [36.09 mm (95% CI: 10.13; 62.05), p=0.0033] demonstrating the superiority of SYNOJOYNT™ to placebo. These results are summarized below in Table 11.

Table 11: Primary analysis on the change of WOMAC pain score from baseline to Week 26 (ITT)

Least Squares (LS) Mean Difference (SE)		Difference from baseline (Saline - SYNOJOYNT™)	2-Sided 95% Lower and Upper Bound of CI	p-value (1-sided)
Saline (n=197)	SYNOJOYNT (n=199)			
-131.64 (9.35)	-167.73 (9.32)	36.09	10.13, 62.05	0.0033

SE : standard error. CI= Confidence Interval of the Difference in Changes

Table 12 below provides additional details of the analysis of the effectiveness dataset at the study assessment timepoints utilizing the repeated measures mixed model.

Table 12: Statistical analysis (Repeated Measures Model) of differences in mean changes from baseline in WOMAC pain scores at 1, 2, 3, 6, 12, 18, and 26 weeks for the ITT population

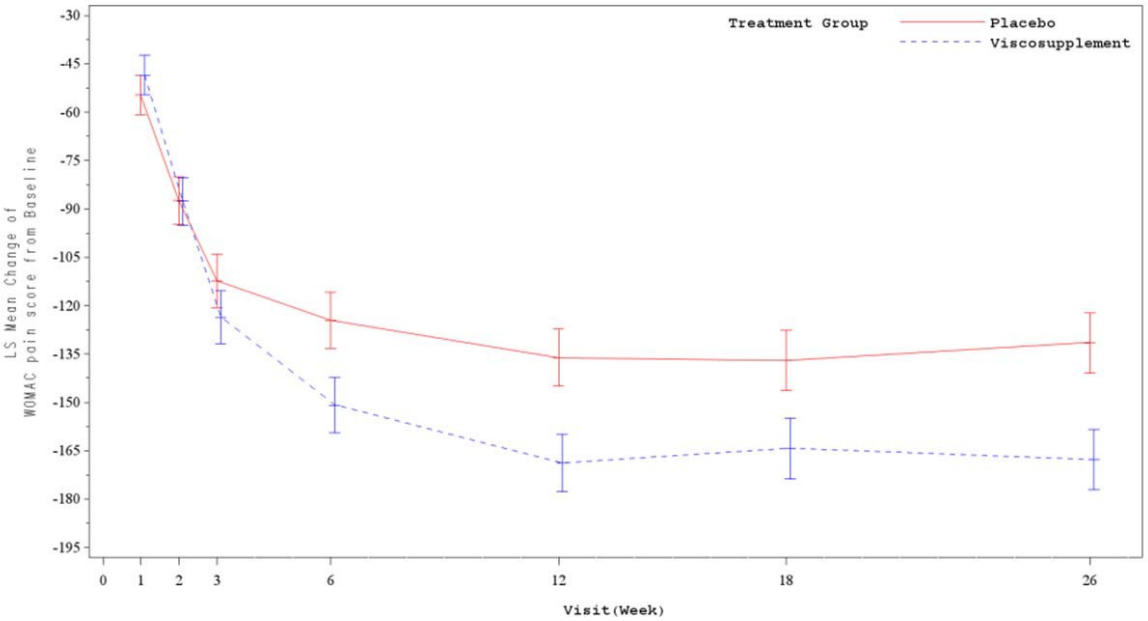
Visit	Treatment	n	LSMean	SD	SE	Difference	SE of Difference	Lower 95%CI	Upper 95% CI
Week 1	Placebo	197	-54.80	84.93	6.05	-6.19	8.56	-23.01	10.63
	SYNOJOYNT™	197	-48.61	84.89	6.05				
Week 2	Placebo	195	-87.58	102.58	7.35	0.23	10.37	-20.16	20.62
	SYNOJOYNT™	197	-87.81	102.72	7.32				
Week 3	Placebo	195	-112.41	115.66	8.28	11.36	11.69	-11.62	34.35
	SYNOJOYNT™	197	-123.78	115.72	8.25				
Week 6	Placebo	194	-124.67	120.60	8.66	26.30	12.24	2.23	50.38
	SYNOJOYNT™	191	-150.98	119.57	8.65				
Week 12	Placebo	189	-137.25	122.63	8.92	32.61	12.61	7.81	57.41
	SYNOJOYNT™	187	-168.86	121.89	8.91				
Week 18	Placebo	187	-137.12	127.40	9.32	27.25	13.22	1.26	53.24
	SYNOJOYNT™	176	-164.30	124.24	9.36				
Week 26	Placebo	189	-131.64	128.52	9.35	36.09	13.20	10.13	62.05
	SYNOJOYNT™	191	-167.73	128.80	9.32				

Note: Results were based on a repeated measures model with the fixed effects of baseline score, treatment,visit,treatment by visit interaction, baseline score by visit interaction, treatment by baseline score interaction; an unstructured covariate matrix was used at each week. SD was calculated by multiplying SE with square root of n at each visit. Higher WOMAC (500mm) scores reflect worse pain function.

CI=confidence interval; ITT=intent-to-treat; LSmean=least squares mean; n=number of subjects assessed at each visit; SD=standard deviation; SE=standard error; WOMAC=Western Ontario and McMaster Universities Arthritis Index (whole 500mm WOMAC Pain Scale).

Figure 1 below graphically depicts the least squares mean change from baseline in WOMAC pain scores for the SYNOJOYNT™ (Viscosupplement) and saline placebo treatment groups with a 36.09 mm difference between the two treatment groups at 26 weeks on the whole 500 mm WOMAC Pain scale.

Figure 1: Least squares mean change from baseline in WOMAC pain score for ITT population



The following secondary effectiveness endpoints were evaluated using SYNOJOYNT™, placebo and EUFLEXXA®:

- The change from baseline in the WOMAC pain score over time
- Pain, stiffness and physical function of the target knee as assessed by WOMAC over time
- The change from Baseline in the Short Form (36) (SF-36) over time.

Over time, the mean percentage change of the WOMAC pain score from baseline was greater for SYNOJOYNT™ compared with placebo. From Week 6 through Week 26 visits, the differences (placebo versus SYNOJOYNT™) in LSmean change of WOMAC pain score from baseline were significantly larger for the SYNOJOYNT™ group versus the placebo group, thus demonstrating superiority of SYNOJOYNT™ to placebo. At Week 6, the difference (placebo versus SYNOJOYNT™) in LSmean of WOMAC pain score from baseline was 26.30 mm (95% CI: 2.23; 50.38) and increased through Week 26 (36.09 mm [95% CI: 10.13; 62.05]).

Over time, the mean percentage change from baseline in the WOMAC stiffness score (200 mm scale) was greater for SYNOJOYNT™ compared with placebo. At Week 26, for the ITT population, the mean percentage change from baseline was higher for SYNOJOYNT™ (-47.37% [SD=45.275]) compared with placebo (-35.77% [SD=63.103]). From Week 2 through Week 26 visits, the magnitude of LSmean change of WOMAC stiffness score from baseline was greater for the SYNOJOYNT™ group versus the placebo group and statistically significantly greater at Weeks 6, 12, and 26 (ITT population).

Over time, the mean percentage change from baseline in the WOMAC stiffness score was similar for SYNOJOYNT™ compared with EUFLEXXA®. At Week 26, for the ITT population, the mean percentage change from baseline was similar for SYNOJOYNT™ (-47.37% [SD=45.275]) compared with EUFLEXXA® (-47.25% [SD=63.020]).

At the Week 26 visit the mean WOMAC Physical Function Score was 659.47 mm (SD=465.305) on the 1700 mm WOMAC Physical Function Score Scale in the placebo group, compared with 566.56 mm (SD=467.059) in the SYNOJOYNT™ group, where a higher WOMAC score reflected worse physical function. At Week 26, for the ITT population, the mean percentage change from baseline was higher for SYNOJOYNT™ (-48.99% [SD=40.163]) compared with placebo (-37.37% [SD=49.555]).

Over time, the mean percentage change from baseline in the WOMAC Physical Function Score was similar for SYNOJOYNT™ compared with EUFLEXXA®. At Week 26, for the ITT population, the mean percentage change from baseline was similar for SYNOJOYNT™ (-48.99% [SD=40.163]) compared with EUFLEXXA® (-53.67% [SD=35.781]).

LSmean increases from baseline in SF-36 Physical Functioning, Bodily Pain, General Health, Vitality, and Role Emotional scores were observed for the SYNOJOYNT™ group versus the placebo group. At Week 26, LSmean increases from baseline in SF-36 were noted for SF-36 Physical Component Summary (PCS), Mental Component Summary (MCS). The observed increases did not reach statistical significance (95% CI for the difference [placebo versus SYNOJOYNT™] included 0).

At baseline, the mean WOMAC Physical Function Score of the target knee was 1096 mm (SD=294.338) in the placebo group compared with 1136 mm (SD=330.307) in the SYNOJOYNT™ group. At the Week 26 visit, the mean WOMAC Physical Function Score was 659 mm (SD=465.305) in the placebo group compared with 567 mm (SD=467.059) in the SYNOJOYNT™ group, where a higher WOMAC score reflects worse physical function.

From the Week 2 through Week 26 visits, the magnitude of the LSmean change of the WOMAC Physical Function Score from baseline was greater for the SYNOJOYNT™ group versus the placebo group and significantly greater at Weeks 6, 12, 18 and 26 (ITT population). Over time, the mean percentage change from baseline was greater for SYNOJOYNT™ compared with placebo. At Week 26, for the ITT population, the mean percentage change from baseline was higher for SYNOJOYNT™ [-48.99% (SD=40.163)] compared with placebo [37.37% (SD=49.555)].

Over time, the mean percentage change from baseline of the WOMAC Physical Function Score was similar for SYNOJOYNT™ compared with EUFLEXXA®. At Week 26, for the ITT population, the mean percentage change from baseline

was similar for SYNOJOYNT™ [-48.99% (SD=40.163)] compared with EUFLEXXA® [-53.67% (SD=35.781)].

Rescue medication use was comparable between treatment groups. From Day 1 through Week 26 the mean (SD) number of acetaminophen caplets administered was 120.6 (SD=141.92), 108.5 (SD=149.59) and 102.1 (SD=124.41) for the placebo group, EUFLEXXA® group and SYNOJOYNT™ group, respectively.

3. Subgroup Analyses
   There were no subgroup analyses.

4. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 33 investigators. None of the clinical investigators had 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.

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

1. Primary Endpoint

   At the Week 26 visit the LS mean change (± SD) from baseline in WOMAC pain scores was -131.64 (9.35) in the placebo group versus -167.73 (9.32) in the SYNOJOYNT™ group. At the Week 26 visit the difference (placebo versus SYNOJOYNT™) in mean change from baseline in WOMAC pain score was significantly greater for the SYNOJOYNT™ group versus the placebo group [36.09

mm (95% CI: 10.13; 62.05), p=0.0033] demonstrating the superiority of SYNOJOYNT™ to placebo.

2. Secondary Effectiveness Endpoints

There were statistically significant differences in the WOMAC Pain score, WOMAC Stiffness score, and WOMAC Physical Function score between the saline placebo and SYNOJOYNT™ treatment groups over 26 weeks, in favor of SYNOJOYNT™. However,there was no statistically significant difference between the EUFLEXXA® and SYNOJOYNT™ treatment groups at any time point over 26 weeks.

The difference (Placebo- SYNOJOYNT™) in reduction of WOMAC stiffness scores between the saline placebo and SYNOJOYNT™ on the 200 mm WOMAC stiffness scale was 11.62mm at 26 weeks, being equivalent to 5.8 mm on the 100 mm WOMAC Stiffness scale, in favor of SYNOJOYNT™ over the saline placebocontrol.

The difference (Placebo- SYNOJOYNT™) in reduction of the WOMAC Physical Function score between the saline placebo and SYNOJOYNT™ at 26 weeks was 103.36mm on the 1700 mm WOMAC Physical Function scale, in favor of SYNOJOYNT™ over the Saline Placebo.

There was no statistically significant difference of any component of SF-36 between the saline placebo and SYNOJOYNT™ at any time point during 26 week period.

B. Safety Conclusions

The risks of the device are based on the pre-clinical laboratory studies, animal studies, as well as data collected in a clinical study conducted to support PMA approval as described above.

The data obtained from the preclinical studies confirmed the biological safety of the SYNOJOYNT™ and demonstrates that the product does not represent a toxicological risk to the patient. These data also established that the product is stable over the claimed shelf life.

Results from the pivotal clinical trial showed comparable adverse events rates between SYNOJOYNT™, the saline placebo, and another commercially available viscosupplement, EUFLEXXA®. Overall, the incidence of TEAEs in the SYNOJOYNT™ treatment group was similar to that of the saline placebo treatment group. In total, 234 (39.3%) subjects experienced 411 TEAEs: 147 TEAEs in the placebo group; 135 TEAEs in the EUFLEXXA® group; and 129 TEAEs in the SYNOJOYNT™ group. In total, 9 (1.5%) subjects (3 [1.5%] subjects placebo group; 1[0.5%] subject EUFLEXXA® group; 5 [2.5%] subjects SYNOJOYNT™ group) had a treatment-emergent SAE.

The three most common device-related TEAEs were injection site joint pain (5 [2.5%] subjects in the placebo group, 1 [0.5%] subjects in the Euflexxa group, 2 [1.0%] subjects in the SYNOJOYNT™ group), arthralgia (2 [1.0%] subjects in the placebo group, 4 [2.0%] subjects in the EUFLEXXA® group, 2 [1.0%] subjects in the SYNOJOYNT™ group) and injection site joint effusion (2 [1.0%] subjects in the placebo group, 1 [0.5%] subjects in the EUFLEXXA® group, 1 [0.5%] subjects in the SYNOJOYNT™ group). The adverse event rates were comparable among the three treatment group and relatively low, and the safety profile of SYNOJOYNT™ was similar to that of the commercially available viscosupplement.

Additional clinical studies have not shown any safety concerns related to its use, including in patients receiving a repeated course of therapy.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Three weekly intra-articular injections of SYNOJOYNT™ provide clinically meaningful benefits for reductions of pain and stiffness and improvement in physical function for patients with osteoarthritis in the knee. The data support the conclusion that the benefits of SYNOJOYNT™ outweigh its risks consisting of fairly low rates of injection site pain and effusion, arthralgia, and other mild transitory adverse events.

1. Patient Perspectives

   Patient perspectives considered during the review included patient-reported assessments consisting of WOMAC Pain scores, WOMAC Stiffness scores and WOMAC Physical Function scores, and other assessments. These assessments provided the basis for evaluation of the primary and secondary effectiveness endpoints of the clinical study used to support the PMA approval of SYNOJOYNT™.

In conclusion, given the available information above, the data support that for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g.,acetaminophen, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The pre-clinical and clinical data contained within the PMA support the reasonable assurance of safety and effectiveness of three weekly intra-articular injections of SYNOJOYNT™ when used in accordance with its labeled indications. Clinical data also support the safe, repeated use of the product. Results from a prospective

randomized, controlled multicenter study showed superiority in effectiveness and similar adverse event profile to a saline placebo control, as well as a comparable safety and effectiveness profiles to that of a commercially available viscosupplement.

XIII. CDRH DECISION

CDRH issued an approval order on May 08, 2018.

The applicant's manufacturing facilities have been inspected 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: See approval order.