SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Sodium Hyaluronate

Device Trade Name: VISCO-3™

Device Procode: MOZ

Applicant's Name and Address: Seikagaku Corporation
6-1, Marunouchi 1-chome Chiyoda-ku,
Tokyo 100-0005, Japan

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P980044/S027

Date of FDA Notice of Approval: December 21, 2015

The original PMA P980044 for SUPARTZ (1% sodium hyaluronate) was approved on January 24, 2001. A new trade name for the device, SUPARTZ FX, was approved under P980044/S025. SUPARTZ FX is a five injection regimen which is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to non-pharmacological therapy and simple analgesics, e.g., acetaminophen. Preclinical data from the original application are applicable for this current supplement for VISCO-3™ (1% sodium hyaluronate) because the technological characteristics and indications for use for VISCO-3 ™ are identical to those of SUPARTZ FX, and the preclinical data from the original application are incorporated by reference here. (VISCO-3 ™ is administered via a three injection regimen as opposed to the five injection regimen for SUPARTZ FX.) Please refer to the SSED for P980044, available on the CDRH website, for additional supporting documentation.

II. INDICATIONS FOR USE

VISCO-3 ™ 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 simple analgesics, e.g., acetaminophen.

III. CONTRAINDICATIONS

- Do not administer to patients with known hypersensitivity (allergy) to sodium hyaluronate preparations.
- Do not inject this product in the knees of patients with infections or skin diseases in the area of the injection site.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the labeling for VISCO-3™.

V. DEVICE DESCRIPTION

VISCO-3™ is a sterile, viscoelastic non-pyrogenic solution of purified, high molecular weight (620,000-1,170,000 daltons) sodium hyaluronate (hyaluronan) having a pH of 6.8-7.8. Each one mL of VISCO-3™ contains 10 mg/mL of sodium hyaluronate (hyaluronan) dissolved in a physiological saline (1.0% solution). The sodium hyaluronate (hyaluronan) is extracted from chicken combs. Sodium hyaluronate (hyaluronan) is a polysaccharide containing repeating disaccharide units of glucuronic acid and N-acetylglucosamine.

Each 2.5 mL prefilled syringe of VISCO-3™ contains:

Sodium Hyaluronate (hyaluronan)	25.0	mg
Sodium Chloride	21.25	mg
Dibasic Sodium Phosphate Dodecahydrate	1.343	mg
Sodium Dihydrogen Phosphate Dihydrate	0.04	mg
Water for Injection		q.s.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of pain emanating from osteoarthritis of the knee. For patients who have failed to respond adequately to conservative non-pharmacologic therapy, nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesics (e.g., acetaminophen), alternative practices and procedures include removal of excess fluid from the knee followed by intra-articular (IA) injection of corticosteroid, exercise, physical therapy, weight loss and avoidance of activities that cause joint pain. For patients who have failed the above treatments, surgical interventions such as arthroscopic surgery and total knee replacement are also alternative treatments. 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

Between 1987 and 2014, marketing approval for use of the SUPARTZ formulation in treatment of osteoarthritic knee pain has been granted in the 16 countries and the European area listed below.

- Japan (1987)
- Korea (1990)*[1]
- Sweden (1992)*[3]
- Finland (1994) *[3]

- Iceland (1994)
- Austria (1995) *[3]
- Italy (1995)
- China (1997)
- Portugal (1997) *[1,*3]
- Denmark (1997) *[3]
- European area (1998) *[2] (the CE marking certification)
- Taiwan (1998)
- Canada (2000)*[1]
- U.S.A. (2001)
- Australia (2002)*[1]
- Philippines (2003)
- New Zealand (2006)*[1]

*[1] SKK withdrew the marketing licenses from these countries for business reasons only. The device has not been withdrawn from marketing for any reason related to safety or effectiveness of the device.

*[2] SKK granted the CE marking certification in European area (member states of the European Union [Austria, Belgium, Denmark, Greece, Germany, Spain, Finland, France, Ireland, Italy, Luxembourg, Netherlands, Portugal, Sweden, United Kingdom (U.K.)] and Switzerland). Of those approved countries, SUPARTZ product was distributed in Belgium, U.K., Germany, Netherlands, Spain, and France until March 2010, but marketing was discontinued thereafter for business reasons, and the SUPARTZ product has been distributed only in Italy for the CE marking.

*[3] SKK granted the marketing licenses both for drugs and the CE marking certification in these countries, and has distributed for drugs.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a comprehensive list of the potential adverse events (e.g., complications) generally associated with intra-articular hyaluronan injections for the treatment of pain in osteoarthritis of the knee:

· Aggravated osteoarthritis
· Arthralgia (knee pain)
· Arthropathy
· Arthrosis
· Baker's cyst
· Bursitis
· Chills
· Dizziness
· Headache
· Hives
· Immune response

· Infection
· Injection site reaction (edema/ erythema/ pain)
· Joint (knee) disorder (effusion/ stiffness/ swelling)
· Localized osteoarthritis
· Malaise
· Muscle cramps
· Nausea
· Pain in limb
· Paresthesia
· Peripheral edema
· Phlebitis
· Pruritus
· Rash
· Tendonitis

Specific to VISCO-3™, the possible adverse reactions that have been reported in the literature and collected as post-marketing experience worldwide include:

· Injection site reactions (pain/ swelling/ effusion/ redness/ warmth)
· Itching
· Swelling of the face, eyelids, mouth and/or extremities
· Rash
· Hives
· Redness in face
· Nausea
· Vomiting
· Fever

Severe injection site reactions have been rarely reported.
Anaphylactic/anaphylactoid reactions accompanied by transient hypotension (sudden drop in blood pressure), all of which resolved either spontaneously or after conservative treatment have been rarely reported.

Literature has also shown that repeated treatment cycles of the VISCO-3™ formulation contain no evidence of an increased safety risk. The frequency and severity of adverse events occurring during repeat treatment cycles did not increase over that reported for a single treatment cycle.

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 a new treatment regimen of the SUPARTZ formulation. Because the technological characteristics and indications for use for VISCO-3™ are identical to those of SUPARTZ FX, no new preclinical testing was required. Data presented in the original PMA (P980044) are considered applicable to address the preclinical requirements of VISCO-3™, and a summary of the preclinical studies conducted in support of the original PMA is available in the SSED for P980044 on the CDRH website. Data from long-term stability and sterility testing presented in the original PMA were supportive of a shelf life of 42 months for VISCO-3™ when stored below 77°F (25°C).

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of three weekly intra-articular injections of VISCO-3™ for the treatment of pain due to OA of the knee in patients who had failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics. The study was performed in the United States (US) under IDE G130271. Data from this clinical study were the basis for the PMA supplement approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between March 28, 2014 and February 3, 2015. The database for this Panel Track Supplement reflected data collected through 12 weeks and included 420 patients. There were 29 investigational sites.

The study was a pivotal, prospective, multi-center, randomized, double-blind, parallel arm, active controlled, and non-inferiority clinical study. The active comparator arm was a commercially available hyaluronan, a legally marketed alternative with identical indications for use.

The primary objective of the study was to demonstrate non-inferiority of VISCO-3™ group to the active control group for the relief of knee joint pain in subjects with OA of the knee as measured by the Western Ontario and McMaster Universities Osteoarthritis Index Visual Analog Scale (WOMAC VAS) (0-100 mm) pain subscale score change from baseline (CFB) over Week 3, Week 6, and Week 12 in the per-protocol set, using mixed model repeated measures (MMRM). The non-inferiority margin was 8% (−8 mm). The statistical test to conclude non-inferiority required the lower bound of the 2-sided 95% confidence interval (CI) around the VISCO-3™ minus the commercially available hyaluronan CFB least square means be greater than −8 mm. The control group was the commercially available hyaluronan.

All subjects diagnosed with OA of the knee who met all inclusion criteria and no exclusion criteria, and who provided written informed consent, were recruited for enrollment into the study. Eligible subjects were randomly assigned in a 1:1 ratio to receive either VISCO-3™ or the active control.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the 13SUP301 study was limited to patients who met the following inclusion criteria:

   Inclusion Criteria

   1. Male or female between the ages of ≥ 40 and ≤ 80 years old.
   2. Clinical evidence of symptomatic OA of the study knee as classified according to Altman criteria. In case of bilateral OA, the Investigator assigned the more severe knee as the study knee (more symptomatic as defined by screening VAS [0-100 mm] WOMAC Index pain subscale score).
   3. The average of the 5 pain questions of the VAS (0-100 mm) WOMAC Index was 41-80 mm, inclusive. Only 1 pain parameter was permitted to be below 20 mm or above 80 mm at baseline (Visit 2).
   4. Symptoms in study knee for at least 1 year prior to the screening visit (Visit 1).
   5. Verified OA of the study knee of Grade 2 or 3 according to a modification of the grading system of Kellgren-Lawrence (K-L) radiographic severity (Grade 2 defined as definite osteophytes with unimpaired joint space; Grade 3 defined as definite osteophytes with moderate joint space narrowing).
   6. Willingness to discontinue NSAIDs (oral and topical) and non-acetaminophen analgesic use 7 days or 5 half-lives prior to the first injection and throughout the study.
   7. Nonprescription nutraceuticals (e.g., glucosamine, chondroitin), topical analgesics (except topical based NSAIDs such as Voltaren® gel and the Flector® Patch), and nasal or inhaled corticosteroids were allowed if the dosage was stable for at least 4 weeks and the regimen was not expected to be increased during the study period. Non-pharmacologic treatments (physical therapy, acupuncture, osteopathic, and chiropractic manipulations) were allowed if treatment was stable for at least 4 weeks and there was no change to the regimen during the study.
   8. Subjects must have been willing to accept "rescue" acetaminophen (≤ 4 g/day) as the only treatment for knee pain during the study and to not take any acetaminophen within 24 hours prior to study visits.
   9. Subjects must not have participated in an investigational study within 30 days of the screening visit or during study participation.

10. All subjects must have provided voluntary written informed consent and been willing to comply with all protocol-required evaluations.

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

Exclusion Criteria

1. Inability to perform a 50 foot walk test.
2. Subjects with rheumatoid arthritis, joint infection, other inflammatory and metabolic arthritis, Lupus or dermatologic disorder or skin conditions in proximity to study knee that would preclude safe IA injections.
3. Prior HA (hyaluronic acid) injections into the study knee within 6 months of the screening visit.
4. IA or intra-muscular steroid injections within 3 months of the screening visit or during study participation. Oral corticosteroids within 4 weeks of the screening visit or during study participation.
5. History of surgical treatment to the study knee or arthroscopic intervention within 3 months prior to the screening visit.
6. Clinically apparent tense effusion of the study knee on examination determined by either a positive bulge sign or positive ballottement of the patella (patellar tap).
7. Fibromyalgia.
8. Osteonecrosis of either knee.
9. Subjects with clinically diagnosed symptomatic OA of the hip.
10. Subjects with any other health condition thought by the Investigator to have potential to interfere with the study participation or assessments, to include: uncontrolled hematological; cardiovascular; neoplastic; pulmonary; neurological; renal; hepatic or systemic disease as well as elective surgeries or planned hospitalizations.
11. Subjects taking greater than 81 mg acetylsalicylic acid daily for the prevention of cardiovascular events. Dose must have remained stable throughout the study.
12. Subjects with known hypersensitivity (allergy) to sodium hyaluronate preparations or acetaminophen.
13. Subjects with known hypersensitivity (allergy) to avian proteins, feathers or egg products.
14. Pregnant or lactating women.

15. Alcohol abuse as determined by the Investigator or use of alcohol for control of pain.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at pre-specified study visits in the pivotal phase that included a screening/Visit 1 (Week −2 to 0), baseline/Visit 2 (Week 0, injection 1), Visit 3 (Week 1, injection 2), Visit 4 (Week 2, injection 3), Visit 5 (Week 3), Visit 6 (Week 6), Visit 7 (Week 12). The subjects of the VISCO-3™ group and active control groups were evaluated for the relief of knee joint pain as measured by the WOMAC VAS (0-100 mm) pain subscale score change from baseline (CFB) over Week 3, Week 6, and Week 12. Adverse events and complications were recorded at all visits.

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

Table 1: Schedule of Study

Assessments	Pivotal Phase (12 Weeks)							Blinded Extension Phase (14 Weeks)	
	Visit 1[1] (Screening)	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9[2]
Study Week	-2 to 0	0 ± 3 days[3]	1 ± 3 days	2 ± 3 days	3 ± 3 days	6 ± 3 days	12 ± 3 days	18 ± 7 days	26 ± 7 days
Informed consent	X								
Inclusion/ Exclusion	X	X							
Demographics and Medical History	X								
K-L Radiographic Grading	X								
Physical examination, VS, weight		X							X[4]
Examination of the Study Knee	X	X	X	X	X	X	X	X	X
Washout of Analgesics		X[5]							
Urine Pregnancy Test		X[6]							
Concomitant Medications/ Therapies	X	X	X	X	X	X	X	X	X

Assessments	Pivotal Phase (12 Weeks)							Blinded Extension Phase (14 Weeks)	
	Visit 1[1] (Screening)	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9[2]
Study Week	-2 to 0	0 ± 3 days[3]	1 ± 3 days	2 ± 3 days	3 ± 3 days	6 ± 3 days	12 ± 3 days	18 ± 7 days	26 ± 7 days
VAS WOMAC Pain Subscale	X[7]	X[8]			X[8]	X[8]	X[8]	X[8]	X[8]
EQ-5D-3L		X			X	X	X	X	X
VAS WOMAC Function subscale		X			X	X	X	X	X
VAS WOMAC Stiffness subscale		X			X	X	X	X	X
Patient Global Assessment		X			X	X	X	X	X
Randomization /IWRS		X							
Intra-articular Injection		X[9]	X[9]	X[9]					
Vital Signs 30 Minutes after Injection		X	X	X					
Instruct subject on rescue medication use, dispense acetaminophen and subject	X	X	X	X	X	X	X	X	
Collect subject diary and reconcile acetaminophen		X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X
Record use of rescue acetaminophen consumption in eCRF[10]		X	X	X	X	X	X	X	X

1 Safety and effectiveness assessments will be performed by the blinded Evaluating Investigator

2 These assessments were also performed for early withdrawals from the study.

3 Study visits will be based on calendar days from Baseline (Week 0). The injection may be given for up to 2 days after the baseline visit as long as injection date is within 14 days from the screening visit. If the Week 0 injection does not occur on the same day as the scheduled baseline study visit, subsequent study

visits will be based on calendar days from the date of the Week 0 injection.
4 Weight only
5 At least 5 half-lives of current analgesic must have passed before the first injection of either the study or reference product.
6 Urine pregnancy test will be performed on all females of childbearing potential
7 WOMAC pain assessment will be based on history of pain in the preceding two weeks.
8 WOMAC pain assessment will be based on subjects' 24hr recall of pain.
9 Intra-articular injection will be administered by unblinded Treating Investigator.
10 No acetaminophen is to be taken for 24 hours before each clinic visit.

3. Clinical Endpoints

With regards to safety, safety assessments performed during the study included documentation of AEs, injection related events, vital signs, knee examinations, and physical examinations. All AEs were collected at each visit. Vital signs were obtained pre and post injection at baseline/Visit 2 (Week 0), Visit 3 (Week 1) and Visit 4 (Week 2). A physical examination was performed at baseline/Visit 2 (Week 0) and during the study exit visit.

With regard to effectiveness, the primary objective of the study was to demonstrate non-inferiority of VISCO-3™ group to the active control group for the relief of knee joint pain in subjects with OA of the knee as measured by the WOMAC VAS (0-100 mm) pain subscale score change from baseline (CFB) over Week 3, Week 6, and Week 12 in the per-protocol set. The non-inferiority margin was 8% (−8 mm). The statistical test to conclude non-inferiority required the lower bound of the 2-sided 95% confidence interval (CI) around the VISCO-3™ minus the commercially available hyaluronan CFB least square means be greater than −8 mm.

B. Accountability of PMA Cohort

At the time of database lock, of 421 patients enrolled in the PMA study, 99.76 % (n=420) of the patients were available for analysis of safety at the completion of the study, the 12-week visit. All safety analyses were performed on the safety set, which included all subjects who received at least one injection. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with at least one AE were classified by system organ class and preferred term.

The per-protocol set used for the effectiveness analysis included all randomized subjects who had at least one post-baseline WOMAC VAS pain subscale score except those with important protocol deviations.

Additional information on subject disposition in the study is provided below in Table 2 and Figure 1.

Table 2: Subject Disposition

	Active Control (N=211) n (%)	VISCO-3™ (N=209) n (%)
Safety Set	211 (99.5)	209 (100.0)
Per-Protocol Set	189 (90.0)	195 (93.8)
Subjects Who Discontinued the Study	21 (10.0)	21 (10.0)
Primary Reason for Discontinuing the Study		
Adverse Event/Adverse Device Effect	4 (1.9)	1 (0.5)
Required Treatment with Excluded Analgesics for Pain Control	4 (1.9)	7 (3.3)
Subject Non-compliance	1 (0.5)	0
Protocol Violation	0	1 (0.5)
Withdrawal of Consent by Subject	4 (1.9)	6 (2.9)
Lost to Follow-up	5 (2.4)	1 (0.5)
Other	3 (1.4)	5 (2.4)

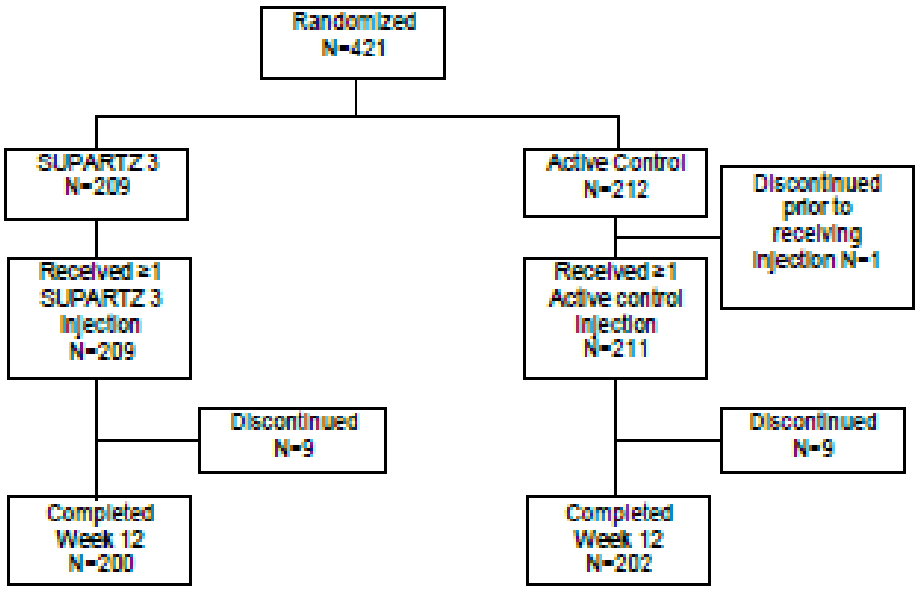

Figure 1: Disposition of Subjects Diagram

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. A total of 586 subjects were screened at 29 US study

centers; 421 subjects were enrolled and 420 subjects received at least one injection of either VISCO-3™ or the active control. Demographic data are shown below in Table 3. There were no statistically significant differences in the demographics between the groups.

Table 3: Demographic Data (Safety set)

Demographic or Baseline Characteristic	Active Control (N=211) n (%)	VISCO-3™ (N=209) n (%)
Age (years)		
n	211	209
Mean (SD)	60.9 (9.33)	59.3 (9.30)
Min-Max	42-80	40-79
Sex (n [%])		
Male	76 (36.0)	71 (34.0)
Female	135 (64.0)	138 (66.0)
Ethnicity (n [%])		
Hispanic or Latino	16 (7.6)	16 (7.7)
Not Hispanic or Latino	195 (92.4)	193 (92.3)
Race (n [%])*		
American Indian or Alaskan Native	0	4 (1.9)
Asian	8 (3.8)	6 (2.9)
Black or African American	41 (19.4)	47 (22.5)
Native Hawaiian or Other Pacific Islander	2 (0.9)	1 (0.5)
White	160 (75.8)	156 (74.6)
Body Mass Index		
n	207	207
Mean (SD)	32.35 (7.174)	33.13 (7.574)
Min – Max	19.9-56.8	15.2-55.0
Baseline WOMAC VAS Pain (mm) (Mean [SD])	58.40 (8.977)	57.83 (9.654)

*A subject could mark more than one race.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 420 subjects that received at least one out of the total of three injections during the period of 12 weeks of evaluation. The key safety outcomes for this study are presented below in Tables 4 to 6. Device-related adverse events (AEs) are reported in Table 6.

Adverse events that occurred in the PMA clinical study:

Adverse events were reported in 51% (107/209) of subjects in the VISCO-3™ group and 52% (109/211) of subjects in the active control group, as summarized below in Table 4. Study device-related AEs were reported in 4% (9/209) of subjects in the VISCO-3™ group and 7% (14/211) of subjects in the active control group. There was one subject in the active control group who died; the AE was not related to the study device. There were 7 subjects who each experienced one serious adverse event (SAE); none were considered related to the study device.

No clinically relevant changes were seen in vital signs or physical examinations.

Table 4: Overall Summary of Treatment-Emergent Adverse Events (TEAEs)

Category	Active Control (N=211) n (%)	VISCO-3™ (N=209) n (%)
Subjects with ≥1 TEAE	109 (51.7)	107 (51.2)
Subjects with ≥1 TEAE related to study device	14 (6.6)	9 (4.3)
Subjects with ≥1 serious adverse event (SAE)	6 (2.8)	1 (0.5)

Treatment-Emergent Adverse Events (TEAEs) occurring in >5% of subjects are summarized below in Table 5 according to numbers and percentages of subjects who experienced one or more TEAEs in each treatment group.

Table 5: TEAEs by System Organ Class and Preferred Term Occurring in >5% of Subjects in Either Treatment Group (Active Control or VISCO-3™)

System Organ Class Preferred Term	Active Control (N=211) n (%)	VISCO-3™ (N=209) n (%)
Musculoskeletal and connective tissue disorders	61 (28.9)	54 (25.8)
Arthralgia	24 (11.4)	23 (11.0)
Back pain	10 (4.7)	15 (7.2)
Nervous system disorders	31 (14.7)	25 (12.0)
Headache	25 (11.8)	22 (10.5)

Note: Subjects with multiple events in the same category are counted only once in that category; subjects with events in multiple categories are counted once in each category.

TEAEs considered to be related to the study device are summarized below in Table 6 according to numbers and percentages of subjects who experienced one or more device-related TEAEs in each treatment group. The most frequently reported specific device-related AEs in the VISCO-3™ group were arthralgia (1%), joint swelling (1.4%), and injection site pain (1.0%).

Table 6: Subjects with Device-Related AE by System Organ Class and Preferred Term

System Organ Class Preferred Term	Active Control (N=211) n (%)	VISCO-3™ (N=209) n (%)
Musculoskeletal and connective tissue disorders	8 (3.8)	6 (2.9)
Joint swelling	3 (1.4)	3 (1.4)
Arthralgia	5 (2.4)	2 (1.0)
Joint instability	1 (0.5)	1 (0.5)
Joint stiffness	1 (0.5)	1 (0.5)
General disorders and administration site conditions	5 (2.4)	3 (1.4)
Injection site pain	0	2 (1.0)
Edema peripheral	2 (0.9)	1 (0.5)
Injection site erythema	1 (0.5)	0
Injection site rash	1 (0.5)	0
Pain	1 (0.5)	0
Nervous system disorders	3 (1.4)	2 (1.0)
Headache	2 (0.9)	1 (0.5)
Neuralgia	0	1 (0.5)
Hemiparesis	1 (0.5)	0
Skin and subcutaneous tissue disorders	1 (0.5)	0
Pruritus	1 (0.5)	0

Note: Subjects with multiple events in the same category are counted only once in that category; subjects with events in multiple categories are counted once in each category.

2. Effectiveness Results

The analysis of effectiveness was based on the 384 evaluable patients over the 12-week time point. Key effectiveness outcomes are presented in Table 7. No secondary endpoints for effectiveness were proposed.

Mean baselines of WOMAC VAS pain subscale were 57.83 mm (standard deviation [SD]: 9.654) in the VISCO-3™ group and 58.40 mm (SD: 8.977) in the active control group. The least squares mean for CFB for VISCO-3™ minus that of the active control over Week 3, Week 6, and Week 12 for WOMAC VAS pain subscale score was −3.30 mm and the 95% CI lower bound of this difference was −6.77 mm. The lower bound −6.77 mm was greater than −8 mm, leading to the conclusion that VISCO-3™ is non-inferior to the active control, as shown in Table 7.

Table 7: Primary Effectiveness Analysis: CFB on the 100 mm WOMAC VAS Pain Subscale Score over Week 3, Week 6, and Week 12 (Per-Protocol Set)

Average over Weeks 3,6, and 12	**Active Control (N=189)**	**VISCO-3™ (N=195)**	**CFB Difference**
Baseline WOMAC VAS Pain (mm) (Mean [SD])	58.40 (8.977)	57.83 (9.654)	
LS Mean (standard error [SE]) of Change from Baseline	30.15 (1.303)	26.85 (1.270)	−3.30 (1.762)
95% CI	27.59-32.71	24.35-29.35	−6.77-0.17

Results at the end of the study (i.e., at Week 12) yielded an average 52.5% reduction in pain for those patients treated with VISCO-3™ (based on a mean CFB of 30.48 mm and mean baseline pain of 57.83 mm).

3. Subgroup Analyses

Subgroup analyses were not performed.

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 29 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

A comparative clinical trial of VISCO-3™ to a commercially available hyaluronan successfully demonstrated non-inferiority within an 8% margin as determined by

comparisons of the change from baseline (CFB) of WOMAC VAS pain subscale scores over the 12 week duration of the trial. The least squares mean for CFB for VISCO-3™ minus that of the active control over Week 3, Week 6, and Week 12 for the WOMAC VAS pain subscale score was −3.30 mm and the 95% CI lower bound of this difference was −6.77 mm and thus was greater than the −8 mm margin required to demonstrate non-inferiority.

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support approval of the PMA supplement as described above. Safety data indicated comparable safety and tolerability of VISCO-3™ to the active control. Of the AEs reported in the clinical study, less than 10% were considered related to the study device in either the VISCO-3™ or active control treatment groups. The most frequently reported specific device-related AEs in the VISCO-3™ treatment group were arthralgia (1%), joint swelling (1.4%), and injection site pain (1.0%). None of the SAEs were considered related to the study device in either group. No clinically relevant changes were observed in vital signs or physical examinations. Overall, these results indicated that VISCO-3™ is safe and well tolerated.

Specific to products with the same formulation as VISCO-3™, the possible adverse reactions that have been reported in the literature and collected as post-marketing experience worldwide include: injection site reactions (pain/ swelling/ effusion/ redness/ warmth); itching; swelling of the face, eyelids, mouth and/or extremities; rash; hives; redness in face; nausea; vomiting; and fever.

Severe injection site reactions have been rarely reported. Anaphylactic/anaphylactoid reactions accompanied by transient hypotension (sudden drop in blood pressure), all of which resolved either spontaneously or after conservative treatment have been rarely reported.

Literature has also shown that repeated treatment cycles of the VISCO-3™ formulation contain no evidence of an increased safety risk. The frequency and severity of adverse events occurring during repeat treatment cycles did not increase over that reported for a single treatment cycle.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support approval of the PMA supplement as described above. Evaluation of the primary effectiveness endpoint for the clinical study showed a difference of –3.30 mm (on the whole 100mm WOMAC VAS pain scale) in mean reductions from baseline pain scores for VISCO-3™ versus a commercially available hyaluronan used as an active control, thus demonstrating that the effectiveness of three injections of VISCO-3™ to be non-inferior to that of three injections of the commercially available hyaluronan at 12 weeks. The mean pain reduction from

baseline for three injections of VISCO-3™ was 26.85mm at 12 weeks on a whole 100mm VAS pain scale, whereas the mean pain reduction for three injections of the control was 30.15 mm. Thus, this non-inferiority study served to demonstrate that the magnitude of the treatment effect for VISCO-3™ was statistically and clinically comparable to that of the commercially available hyaluronan approved for the same indication for use.

The clinical data showed that adverse events for the VISCO-3™ treatment group in the study were infrequent, mild, and transient in nature. The most frequently reported of these non-serious and transient adverse events for the VISCO-3™ treatment group were arthralgia (1%), joint swelling (1.4%), and injection site pain (1.0%). These AE rates in the study population are typical of those for viscosupplement devices for treatment of knee pain due to OA and are accepted and well tolerated by patients given the probable benefits of these devices. In addition, these non-serious adverse events can be addressed in a straightforward manner with pain medication, topical ointments, etc. Overall, the risk of this device can be categorized as minimal or negligible.

In conclusion, given the available information above, the data and analyses support that for the indication for use 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), the probable benefits of VISCO-3™ 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 primary analysis confirmed that treatment with 3 injections of VISCO-3™ administered once a week (1 week apart) was non-inferior to 3 injections of a commercially available hyaluronan administered once a week (1 week apart) for treatment of OA knee pain over 12 weeks. The safety results for VISCO-3™ were consistent with those of the commercially available hyaluronan and typical of those of approved viscosupplement devices in general.

XIV. CDRH DECISION

CDRH issued an approval order on December 21, 2105.

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.