SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Hyaluronic Acid

Device Trade Name: Gel-One®

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: P080020/S020

Date of FDA Notice of Approval: September 27, 2016

The original PMA (PMA 080020) was approved on March 22, 2011, and is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to non-pharmacologic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics, e.g., acetaminophen.

The current supplement was submitted to revise the labeling to expand the duration from 13 to 26 weeks for reasonable assurance of the safety and effectiveness of treatment from a single injection of Gel-One®. Preclinical data from the original PMA application are applicable for this current supplement because the technological characteristics and indications for use are identical to those of the device as approved under P080020. Accordingly, the preclinical data from the original application are incorporated by reference here. Please refer to the SSED for P080020, available on the CDRH website, for additional supporting documentation.

II. INDICATIONS FOR USE

Gel-One® is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to non-pharmacologic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics, e.g., acetaminophen.

III. CONTRAINDICATIONS

- Do not administer Gel-One® to patients with known hypersensitivity (allergy) to Gel-One® or sodium hyaluronate preparations.

- Do not inject Gel-One® in the knees of patients having skin diseases or infections in the area of the injection site.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the labeling for Gel-One®.

V. DEVICE DESCRIPTION

Gel-One® is a sterile, transparent and viscoelastic hydrogel composed of cross-linked hyaluronate, a derivative of highly purified sodium hyaluronate (hyaluronan) extracted from chicken combs. Hyaluronan is a polysaccharide containing repeating disaccharide units of glucuronic acid and N-acetylglucosamine.

Gel-One® is delivered in a single-use, pre-filled disposable glass syringe. This pre-filled syringe is composed of a rubber piston [butyl rubber: latex free], rubber tip cap [butyl rubber: latex free], finger grip and plunger rod and is packaged in a molded plastic amorphous polyethylene terephthalate (A-PET) film blister with a Tyvek® lid.

Each pre-filled syringe with 3 mL of Gel-One® contains:

Cross-linked Hyaluronate	30.0 mg
Sodium Chloride	24.3 mg
Dibasic Sodium Phosphate Dodecahydrate	0.89 mg
Sodium Dihydrogen Phosphate Dihydrate	1.93 mg
Water for Injection	q.s. to 3mL

Each package contains 1 blister-packed syringe and product information (a package insert).

Gel-One® is provided sterile and has a shelf life of 12 months if stored in the original package below 77°F (25°C).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of pain emanating from OA of the knee in patients who have failed to respond adequately to non-pharmacologic therapy, NSAIDs or analgesics. Alternative practices and procedures include removal of excess fluid from the knee followed by intra-articular injection of a 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

Gel-One received PMA approval under P080020 on March 22, 2011. It has only been marketed within the US. The device has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) 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

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.

Specific to Gel-One®, 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 eyelids and/or extremities
- Rash
- Hives
- Nausea

Literature has also shown that repeated treatment cycles of the Gel-One® 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 NONCLINICAL STUDIES

This supplement presented clinical data to support revision of the labeling of Gel-One® to expand the duration from 13 to 26 weeks for reasonable assurance of the safety and effectiveness of treatment from a single injection. Since the technological characteristics and indications for use of the device are identical to those of the device as approved under P080020, no new preclinical testing was required. Data presented in the original PMA, P080020, are considered applicable to address the preclinical requirements of Gel-One®, and a summary of the preclinical studies conducted in support of the original PMA is available in the SSED for P080020 on the CDRH website.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

26-Week Safety and Effectiveness Study (Gel/1133)

Study Gel/1133 was a phase 3, multicenter, randomized, double-blinded, phosphate-buffered saline (PBS)-controlled study with an open-label extension repeat-injection phase conducted under IDE # G130078. The predefined purpose of the Gel/1133 study was to evaluate the safety and effectiveness of a single intra-articular injection of Gel-One® over 26 weeks.

A summary of the initial double-blinded phase of this clinical study is presented below.

A. Study Design

Patients were enrolled between August 13, 2013, and February 19, 2015. The database for this Panel Track Supplement reflected data collected through September 2, 2015, and included 814 patients. There were 38 investigational sites.

The study was a pivotal, prospective, multicenter, randomized, double-blinded, parallel arm, placebo controlled and superiority clinical study intended to evaluate the safety and effectiveness of a single injection of Gel-One® over 26 weeks. Phosphate-buffered saline (PBS) was utilized as the placebo control.

Study Gel/1133 was conducted at 38 sites in the US. Subjects were between the ages of 40 and 80 years and had diagnosed OA of the knee as determined by a K-L score of grade 1 to 3 and a pretreatment pain score of 50 to 90 mm on a 100-mm VAS in the target knee following a 50-foot walk test. Baseline pain in the contralateral knee following the walk test had to be graded as less than 30 mm on the VAS. Subjects could have no serious systemic diseases. All subjects who completed the initial injection phase were eligible for a repeat injection.
Following screening, 817 subjects were randomized in a 1:1 ratio to treatment with Gel-One® or PBS. Randomization was balanced using site, K-L score, and pretreatment average 50-foot walk test score for the target knee. Screening occurred 1 to 2 weeks prior to Baseline (Week 0). Subjects who agreed to wash out any prohibited medication(s) or needed to stabilize their dose of a permitted concomitant medication(s) were allowed to remain in the study and return after 30 days. Subjects were randomized to receive a single injection of Gel-One® or PBS administered by an unblinded injecting physician at Week 0, after which they were followed for 26 weeks. Subjects returned for clinic visits at Weeks 3, 6, 12, 18, and 26.

At all visits, a blinded evaluating physician, or a back-up blinded evaluating physician, conducted the assessments. Subjects reported their pain on a 100-mm VAS after a 50-foot walk test and completed the WOMAC and a patient global evaluation at all visits. In addition, the SF-36 was completed at Baseline and at Week 26. The blinded evaluating physician completed a physician global evaluation and an examination of the target knee at all visits. Acetaminophen was provided as rescue medication, and tablet counts were used to assess consumption between visits.

The double-blinded phase of the study lasted approximately 25 months. The first subject was enrolled on August 13, 2013, and the last subject completed the study on September 2, 2015.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Gel/1133 study was limited to patients who met the following inclusion criteria:

   1) Provided signed written informed consent.

   2) Was willing and able to complete effectiveness and safety questionnaires and was able to read and understand study instructions.

3) Was a male or female aged 40 to 80 years (inclusive) at the time of informed consent.

4) Had knee pain in the target knee for most of the previous 30 days.

5) Had a grade 1 to 3 score on the K-L grading scale and had radiographic evidence of one or more of the following features in the target knee by bilateral standing anteroposterior (AP) x-ray taken no longer than 90 days prior to screening:

   a. Osteophytes

   b. Joint space narrowing

   c. Osteosclerosis

6) Could complete the 50-foot walk test (without assistance and with no time constraint).

7) Had a pain score for the target knee of 50 mm to 90 mm (inclusive) recorded on a 100-mm VAS immediately following a 50-foot walk at both screening and Week 0 preinjection (Visits 1 and 2).

8) Had an averaged pain score for the contralateral knee of less than 30 mm recorded on a 100-mm VAS immediately following a 50-foot walk at screening and Week 0 preinjection (Visits 1 and 2).

9) Had been on a stable dose of any allowed, long-term concomitant medications and a stable regimen of non-pharmacological therapies for 30 days prior to screening, including the following:

   a. Allowed concomitant medications
      - Antidepressants for depression or anxiety
      - Chondroitin sulfate, oral HA, or/and glucosamine

   b. Non-pharmacological therapies

   Subjects were encouraged to remain on a stable dose of any of these medications throughout the study. Subjects not meeting this criterion could return after 30 days on a stable dose of these medications to complete the screening process.

10) Was willing to discontinue use of any of the following prohibited medications:

    a. Opioids, including but not limited to the following:

- Morphine
- Codeine
- Hydromorphone
- Hydrocodone
- Meperidine
- Oxycodone
- Oxymorphone
- Propoxyphene
- Tramadol
- Buprenorphine
- Butorphanol
- Nalbuphine
- Pentazocine

b. Long-acting opioid patches, such as tramadol and fentanyl

c. Long-acting formulations of oral opioids, such as oxycodone, methadone, and levorphanol

d. Corticosteroids administered by any route, with the exception of intranasal corticosteroids and steroid-containing ophthalmic solutions

Subjects who agreed to discontinue use of a prohibited medication could return after 30 days to complete the screening process.

11) Was willing to switch to using acetaminophen as a rescue medication if currently using other pain medications, such as NSAIDs, or if currently using anticonvulsants exclusively for pain management. A maximum of 1,000 mg/day of acetaminophen was permitted for breakthrough pain control. The use of low-dose aspirin (one to two 81-mg doses/day) for thrombosis prophylaxis was permitted.

12) Was willing to suspend the use of all medications for pain including acetaminophen (except antidepressants for depression or anxiety) and non-pharmacologic therapies to treat knee pain (e.g., physical therapy, ice or heat packs) for 24 hours before each study visit.

Patients were <u>not</u> permitted to enroll in the Gel/1133 study if they met any of the following exclusion criteria:

1) Had any of the following:

a. Grade 4 score on the K-L grading scale for the target knee.

b. Grade 3 score on the K-L grading scale for the target knee and exhibited at least one characteristic of a grade 4 on the radiograph (large osteophytes,

marked narrowing of joint space, severe sclerosis, or definite deformity of bone contour).

c. Acute fracture of the lower limb.

d. Medical history of severe bone disease (e.g., osteoporosis, osteonecrosis, joint deformity, meniscal instability, or septic arthritis).

2) Was categorized as grossly obese, defined as body mass index (BMI) greater than 35 kg/m^2.

3) Had clinically apparent tense effusion of the target knee.

4) Had chondrocyte transplantation or reconstruction of ligaments in the target knee.

5) Had received an intra-articular HA injection(s) for the treatment of OA of either knee within 6 months prior to screening.

6) Had received an intra-articular injection(s) into any joint (e.g., corticosteroids or chondroprotective agents) within 90 days prior to screening. Subjects receiving a corticosteroid injection during the study were withdrawn from the study.

7) Began treatment with or changed the dosage of an allowed concomitant medication within 30 days prior to screening. Subjects could return after 30 days on a stable dose of these medications.

8) Had surgery to the target knee within 12 months or arthroscopy of the target knee within 90 days prior to screening.

9) Had a joint replacement of the target knee at any time. Joint replacement of the contralateral knee was permitted provided it was performed at least 12 months prior to screening.

10) Had significant joint infection in the target knee or inflammatory or skin disorder in the injection area of the target knee.

11) Had symptomatic OA of the hips, spine, or ankle, if it would interfere with the evaluation of the target knee.

12) Had an inflammatory disease of either knee other than OA (e.g., rheumatoid arthritis, septic arthritis).

13) Had another disease that could affect the health of the knee (e.g., chronic hemochromatosis; sickle cell anemia; arthropathies of systemic diseases such

as chondrocalcinosis, gout, pseudogout, psoriasis, hemophilia, and infectious diseases of the joints).

14) Had fibromyalgia, anserine bursa, lumbar radiculopathy, neurogenic or vascular claudication, vascular insufficiency of lower limbs, or peripheral neuropathy severe enough to interfere with the study evaluations.

15) Was hospitalized at the time of screening or had a planned hospitalization during the life of the study.

16) Had a known history of allergy to HA products or acetaminophen.

17) Had contraindications to treatment with acetaminophen.

18) Had a history of recurrent, severe allergic or immune-mediated reactions or other autoimmune disorders.

19) Had a malignancy at the time of screening or had received treatment for malignancy within the past 5 years.

20) Had used an investigational drug, device, or biologic in the 90 days prior to screening.

21) Had a systemic or other disease or significant liver function test results from screening that, in the opinion of the investigator, would interfere with study evaluation or have an impact on the balance of benefits and risks of study treatment.

    a. Diseases that could have interfered: uncontrolled diabetes; immunodeficiency syndrome; significant cardiovascular, renal, or liver disease; severe anemia; severe thrombocytopenia; or severe infectious disease with or without fever.

    b. Significant liver function test results: aspartate amino transferase (AST) or alanine amino transferase (ALT) greater than 2.5 times the upper limit of normal.

22) Female subjects who were pregnant or lactating.

23) Female subjects of childbearing potential who were not willing to use adequate contraceptive measures to avoid pregnancy. All sexually active subjects agreed to practice an adequate method of birth control during the study. Adequate methods of birth control included the following:

    a. Hormonal contraception.

b. Use of at least one acceptable barrier method. Acceptable barrier methods included diaphragm plus a spermicidal agent or condoms (male or female) plus a spermicidal agent.

c. Vasectomy, hysterectomy, bilateral tubal ligation, intrauterine device, and/or an exclusive sexual partner for whom one of these methods applies.

Females who had not menstruated within the past 2 years were considered postmenopausal and did not need to practice birth control.

24) Any psychiatric illness or history of alcohol or other substance abuse that would prevent comprehension of the details and nature of the study.

25) Any subject who was receiving worker's compensation or was involved in litigation at the time of screening.

26) Any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at Weeks 3, 6, 12, 18, and 26 post-treatment. Subjects reported their pain on a 100-mm VAS after a 50-foot walk test and completed the WOMAC and a patient global evaluation at all visits. In addition, the SF-36 was completed at Baseline and at Week 26. The blinded evaluating physician completed a physician global evaluation and an examination of the target knee at all visits. Acetaminophen was provided as a rescue medication, and tablet counts were used to assess consumption between visits. Adverse events and complications were recorded at all visits.

Additional details for the assessments performed at the screening visit, the baseline visit, and the follow-up visits are provided below in Table 1.

Table 1. Schedule for Procedures and Evaluation

Visit Number	**Screening**	**Baseline**	**Follow-up**				
	1	**2**	**3**	**4**	**5**	**6**	**7**
Week	-2 to -1[1]	0	3	6	12	18	26
Window (week)			±1	±1	±1	±1	±1
Informed Consent	X						
Eligibility Assessments	X	X					
X-ray[2]	X						

Vital Signs	X						
BMI (Height, Weight)	X						
Medical History	X	X					
Prohibited Medications/ Therapies[3]	X	X					
Pregnancy Test	X						
Laboratory Tests	X						
Concomitant Medications[3]	X	X	X	X	X	X	X
Adverse Events[4]	X	X	X	X	X	X	X
Acetaminophen Consumption Assessment		X	X	X	X	X	X
WOMAC Osteoarthritis Index[5]	X	X	X	X	X	X	X
SF-36		X					X
Target Knee Examination	X	X	X	X	X	X	X
50-foot Walk Test[5]	X	X	X	X	X	X	X
Patient Global Evaluation[5]	X	X	X	X	X	X	X
Physician Global Evaluation[5]	X	X	X	X	X	X	X
Inclusion/ Exclusion Criteria	X	X[6]					
Randomization[7]		X					
Injection		X					
Distribute Acetaminophen	X	X	X	X	X	X	
End of Study Form[8]							X

AE = adverse event; BMI = body mass index; SF-36 = Short Form (36) Health Survey; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

1 Visit 2 (Week 0) occurred within a 1- to 2-week window of Visit 1 (Screening).

2 X-ray was required if subjects had not had an x-ray within 3 months of Visit 1 (Screening).

3 Subjects who agree to wash out any prohibited medication(s) or need to stabilize their dose of an allowed concomitant medication(s) remained in the study and returned after 30 days to undergo

Visit 1 (Screening) for a second time.

4 Adverse events were assessed twice at each in-person study visit: once at the beginning to capture AEs that occurred since the last study visit, and once at the end to capture any AEs resulting from the study procedures.

5 Baseline score for these assessments was the averaged score at Visit 1 (Screening) and Visit 2 (Week 0).

6 At Visit 2, baseline scores and laboratory test results were confirmed prior to injection.

7 Subjects were randomized to Gel-One® or phosphate-buffered saline.

8 The end of study form was completed at Visit 7 for those subjects who chose not to continue into the repeat injection phase of the study.

3. Clinical Endpoints

The primary safety objective of the study was to demonstrate reasonable assurance of the safety of a single injection of Gel-One® over 26 weeks by examining the incidence of treatment emergent adverse events (TEAEs). Adverse events were categorized using a standardized coding dictionary (i.e., Medical Dictionary for Regulatory Activities [MedDRA]). Incidence rates of TEAEs were compared for those subjects treated with Gel-One® and those subjects receiving the injection of PBS.

Overall TEAEs, TEAEs related to study treatment, and TEAEs by severity were summarized along with the numbers and percentages of subjects who experienced any injection site reaction, any adverse event resulting in discontinuation, any serious adverse events (SAEs), and unanticipated adverse device effects (UADEs). The number of TEAEs and the number and percentage of subjects with events were summarized by system organ class and preferred term; similar presentations were prepared by relationship and maximum severity. Subjects were counted once in each system organ class and preferred term. Percentages were based on the total number of treated subjects in the treatment group. The number and percentage of subjects reporting swelling, redness, or effusion were presented by treatment for each visit. Vital signs at screening were summarized descriptively using the conventions for continuous variables. No imputation of missing values was performed for safety data.

The primary effectiveness objective of the study was to demonstrate a clinically meaningful reduction in pain due to OA of the knee, as measured by a 50-foot walk test, over a 26-week evaluation period in subjects treated with Gel-One® compared with subjects treated with PBS. The primary effectiveness objective was tested using the null hypothesis that there is no difference in the mean change from the pretreatment measure of pain relief (50-foot walk test) between Gel-One® and PBS over 26 weeks. The group comparison was defined as the average effect over Weeks 3, 6, 12, 18, and 26. The basic longitudinal model was specified as a repeated measures model that expressed the pain score as a linear function of treatment, time, treatment-by-time interaction, clinically relevant covariates (baseline pain measurement and Kellgren-Lawrence [K-L] score), and a fixed site effect. Time was considered a categorical variable.

The secondary effectiveness objectives of the study were to analyze the effect of Gel-One® on pain due to OA of the knee over a 26-week evaluation period as assessed by the following:

- Outcome Measures in Rheumatology – Osteoarthritis Research Society International (OMERACT-OARSI) responder rate
- WOMAC pain subscore
- WOMAC total score
- WOMAC physical function subscore
- WOMAC stiffness subscore
- Physician global evaluation
- Patient global evaluation
- Short Form (36) Health Survey (SF-36) physical component score
- Use of acetaminophen rescue medication

The OMERACT-OARSI responder rate was tested using the null hypothesis that there was no difference in OMERACT-OARSI responder rate between Gel-One® and PBS over 26 weeks. The other secondary effectiveness objectives above were tested in a manner similar to the primary effectiveness objective, using the null hypothesis that there was no difference in the mean change from the pretreatment measure of a secondary effectiveness objective between Gel-One® and PBS over 26 weeks.

B. Accountability of PMA Cohort

A total of 1595 subjects were screened. Overall, 817 subjects were randomized, 410 subjects to PBS and 407 subjects to Gel-One®; all but 3 of these subjects, who were randomized but not injected, composed the safety population (Table 2).

Most randomized subjects (87.1%) completed the double-blind phase of the study, with 102 of 817 subjects discontinuing prematurely. The most common reasons for discontinuation were withdrawal by the subject (27.5% of discontinued subjects), lost to follow-up (20.6%), and adverse event (16.7%). The Gel-One® and PBS groups were generally comparable with respect to composition.

Table 2. Summary of Subject Disposition

	PBS (N = 410) n (%)	**Gel-One® (N = 407) n (%)**	**All Treatments (N = 817) n (%)**
Screened			1595
Randomized	410	407	817
Analysis populations[a]			
Safety	410 (100.0)	404 (99.3)	814 (99.6)
Intent-to-treat	407 (99.3)	402 (98.8)	809 (99.0)
Per-protocol	385 (93.9)	369 (90.7)	754 (92.3)

Safety population[a]			
Completed	356 (86.8)	356 (87.5)	712 (87.1)
Discontinued	54 (13.2)	48 (11.8)	102 (12.5)
Reason for discontinuation[b]			
Adverse event	8 (14.8)	9 (18.8)	17 (16.7)
Lost to follow-up	14 (25.9)	7 (14.6)	21 (20.6)
Noncompliance with study protocol	8 (14.8)	5 (10.4)	13 (12.7)
Protocol violation	0 (0.0)	4 (8.3)	4 (3.9)
Investigator decision	2 (3.7)	1 (2.1)	3 (2.9)
Withdrawal by subject	13 (24.1)	15 (31.3)	28 (27.5)
Lack of efficacy	7 (13.0)	6 (12.5)	13 (12.7)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (3.7)	1 (2.1)	3 (2.9)
Entered open-label extension phase[a]	218 (53.2)	208 (51.1)	426 (52.1)

Note: Three subjects were randomized, but not injected, and therefore are not included in the safety population.

a Percentages are based on the number of subjects in each treatment group who were randomized.

b Percentages are based on the number of subjects in each treatment group who discontinued.

As shown in Table 3, the majority of subjects (>85%) in both treatment groups attended each visit in the double-blind phase of the study. Visit 3, the first follow-up visit, was attended by 405 (98.8%) subjects in the PBS group and 400 (98.3%) subjects in the Gel-One® group. Visit 7, the final visit in the double-blind phase occurring 26 weeks following injection, was attended by 364 (88.8%) subjects in the PBS group and 363 (89.2%) subjects in the Gel-One® group.

Table 3. Summary of Subject Disposition by Double-Blind Visit

	PBS (N = 410) n (%)	**Gel-One® (N = 407) n (%)**	**All Treatments (N = 817) n (%)**
Randomized	410	407	817
Attended Screening (Visit 1)	410 (100.0)	407 (100.0)	817 (100.0)
Attended Baseline (Visit 2)	410 (100.0)	404 (99.3)	814 (99.6)
Attended Week 3 (Visit 3)	405 (98.8)	400 (98.3)	805 (98.5)
Attended Week 6 (Visit 4)	398 (97.1)	395 (97.1)	793 (97.1)
Attended Week 12 (Visit 5)	389 (94.9)	382 (93.9)	771 (94.4)
Attended Week 18 (Visit 6)	376 (91.7)	372 (91.4)	748 (91.6)
Attended Week 26 (Visit 7)	364 (88.8)	363 (89.2)	727 (89.0)

Table 4 summarizes the analysis sets used in this report. The safety analysis set consisted of all randomized subjects who received the study injection and totaled 814 subjects (99.6% of randomized subjects). The intent-to-treat (ITT) population comprised 809 subjects (99.0% of randomized subjects) who received the study injection and had data from at least 1 post-injection visit. All effectiveness analyses were based on the ITT population, except where noted. The PP population consisted of 754 subjects (92.3% of randomized subjects) who received the study injection, had at

least 1 post-injection visit, and had no major protocol violation(s). The PP population was utilized for sensitivity analysis of the effectiveness endpoints as noted. The treatment groups were comparable with respect to the proportion of subjects in each analysis set.

Table 4. Summary of Analysis Populations

	PBS (N = 410) n (%)	**Gel-One® (N = 407) n (%)**	**All Treatments (N = 817) n (%)**
Randomized	410	407	817
Included in safety	410 (100.0)	404 (99.3)	814 (99.6)
Excluded from safety	0 (0.0)	3 (0.7)	3 (0.4)
Not injected	0 (0.0)	3 (100.0)	3 (100.0)
Included in intent-to-treat	407 (99.3)	402 (98.8)	809 (99.0)
Excluded from intent-to-treat	3 (0.7)	5 (1.2)	8 (1.0)
Did not have any post-baseline assessments	3(100.0)	2 (40.0)	5 (62.5)
Not injected	0 (0.0)	3 (60.0)	3 (37.5)
Included in per-protocol	385 (93.9)	369 (90.7)	754 (92.3)
Excluded from per-protocol	25 (6.1)	38 (9.3)	63 (7.7)
Did not have any post-baseline assessments	3 (12.0)	2 (5.3)	5 (7.9)
Not injected	0 (0.0)	3 (7.9)	3 (4.8)
Protocol deviation	22 (88.0)	33 (86.8)	55 (87.3)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population were typical for a study performed in the US of reduction of pain due to osteoarthritis.

Table 5 summarizes the demographic characteristics of the ITT population. Slightly more than half of subjects (56.2%) were female. The majority of subjects were White (64.8%); the other major races represented were Black or African American (20.1%) and Asian (12.9%). The majority of subjects (92.2%) were not Hispanic or Latino. The mean age was 59.6 years. The demographic characteristics of the Gel-One® and PBS treatment groups were similar.

Table 5. Summary and Comparison of Demographic Characteristic by Treatment Group – ITT Population

Characteristic Category or Statistic	**PBS (N = 407)**	**Gel-One® (N = 402)**	**All Treatments (N = 809)**
Sex – n (%)			
Male	173 (42.5)	181 (45.0)	354 (43.8)
Female	234 (57.5)	221 (55.0)	455 (56.2)
Age (years)			
N	407	402	809
Mean	59.8	59.3	59.6
SD	9.32	9.14	9.23
Race – n (%)			
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	52 (12.8)	52 (12.9)	104 (12.9)
Black or African American	70 (17.2)	93 (23.1)	163 (20.1)
Native Hawaiian or Pacific Islander	1 (0.2)	0 (0.0)	1 (0.1)
White	277 (68.1)	247 (61.4)	524 (64.8)
Other	7 (1.7)	10 (2.5)	17 (2.1)
Ethnicity – n (%)			
Not Hispanic or Latino	379 (93.1)	367 (91.3)	746 (92.2)
Hispanic or Latino	28 (6.9)	35 (8.7)	63 (7.8)

Table 6 summarizes baseline characteristics for the ITT population. The mean BMI was 28.698. Overall, 40.2% (325/809) of subjects had a K-L score of 2, 32.1% (260/809) of subjects had a K-L score of 3, and 27.7% (224/809) of subjects had a K-L score of 1. Subjects' mean knee OA disease duration prior to the study was 6.85 years. The majority (88.8%) of subjects reported their OA etiology as idiopathic rather than post-traumatic. The study knees of the subjects were split approximately equally between the right and left knees (right: 52.0%). All of these baseline characteristics were similar between the Gel-One® and PBS treatment groups.

The mean baseline 50-foot walk test VAS for the study knee was 69.25 mm for the Gel-One® group and 69.36 mm for the PBS group. The mean baseline 50-foot walk test VAS for the contralateral knee was 11.50 mm for the Gel-One® group and 11.95 mm for the PBS group. The VAS scores were similar between the Gel-One® and PBS groups for both knees.

Table 6. Summary and Comparison of Baseline Characteristics by Treatment Group – ITT Population

Characteristic Statistic or Category	**PBS (N = 407)**	**Gel-One® (N = 402)**	**All Treatments (N = 809)**
Body mass index (kg/m^2)			
N	407	402	809
Mean	28.797	28.597	28.698
SD	3.9244	4.1923	4.0585
Kellgren-Lawrence score			
1	111 (27.3)	113 (28.1)	224 (27.7)
2	164 (40.3)	161 (40.0)	325 (40.2)
3	132 (32.4)	128 (31.8)	260 (32.1)
Osteoarthritis knee disease duration			
N	407	402	809
Mean	6.90	6.80	6.85
SD	7.072	7.835	7.456
Etiology			
Idiopathic	359 (88.2)	359 (89.3)	718 (88.8)
Post-traumatic	48 (11.8)	43 (10.7)	91 (11.2)
Study knee			
Right	212 (52.1)	209 (52.0)	421 (52.0)
Left	195 (47.9)	193 (48.0)	388 (48.0)
50-Foot walk test VAS pain score (baseline)			
N	407	402	809
Mean	69.36	69.25	69.31
SD	7.817	7.640	7.725
50-Foot walk test contralateral VAS pain			
N	407	402	809
Mean	11.95	11.50	11.73
SD	7.565	7.536	7.549

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety analysis set of 814 subjects (99.6% of randomized subjects) and was based upon a comparison of incidence rates of TEAEs over 26 weeks for those subjects treated with Gel-One® and those subjects receiving the PBS injection.

Adverse effects that occurred in the PMA clinical study:

Table 7 below presents an overall summary of TEAEs for the safety analysis set. During the double-blind phase of the study, 382 (46.9%) of 814 subjects reported 842 TEAEs, with the incidence being similar between the Gel-One® and PBS treatment groups (45.8% and 48.0%, respectively). The majority of TEAEs were mild in severity (586/842 events) and were judged by the investigator not to be related to Gel-One® (761/842 events). A total of 14 serious TEAEs were reported for 13 subjects, all of which were deemed by the investigator to be unrelated to study treatment. Overall, according to the analyzed datasets, 20 subjects reported 30 TEAEs that resulted in discontinuation from the study. No deaths or UADEs were reported in the double-blind phase of this study.

Table 7. Overall Summary of Treatment-Emergent Adverse Events – Safety Population

	PBS (N = 410) n (%)		**Gel-One® (N = 404) n (%)**		**All Treatments (N = 814) n (%)**		
	n (%)	**Events**	**n (%)**	**Events**	**n (%)**	**Events**	**P-Value**
TEAEs	197 (48.0)	421	185 (45.8)	421	382 (46.9)	842	0.528
Deaths	0	0	0	0	0	0	NA
Serious TEAEs	6 (1.5)	7	7 (1.7)	7	13 (1.6)	14	0.787
Related	0	0	0	0	0	0	NA
Not Related	6 (1.5)	7	7 (1.7)	7	13 (1.6)	14	
TEAEs Leading to Withdrawal	10 (2.4)	14	10 (2.5)	16	20 (2.5)	30	>0.999
Injection Site Reactions	10 (2.4)	11	11 (2.7)	15	21 (2.6)	26	0.829
Related	8 (2.0)	9	5 (1.2)	8	13 (1.6)	17	0.578
Not Related	2 (0.5)	2	6 (1.5)	7	8 (1.0)	9	
UADEs	0	0	0	0	0	0	NA
Severity							
Mild	127 (31.0)	302	105 (26.0)	284	232 (28.5)	586	
Moderate	60 (14.6)	108	67 (16.6)	113	127 (15.6)	221	0.322
Severe	10 (2.4)	11	13 (3.2)	24	23 (2.8)	35	0.533
Relationship							

Related	27 (6.6)	42	25 (6.2)	39	52 (6.4)	81	0.886
Not Related	170 (41.5)	379	160 (39.6)	382	330 (40.5)	761	

Table 8 below summarizes the most frequent TEAEs reported in the safety population. Treatment-emergent adverse events were reported in 185 subjects (45.8%) in the Gel-One® treatment group and in 197 subjects (48.0%) in the PBS treatment group. The incidences of TEAEs in the most common system organ classes were similar between the Gel-One® and PBS treatment groups.

The most commonly reported (incidence >5% of subjects in either treatment group) preferred terms of TEAEs were arthralgia (10.6%), joint swelling (9.2%), and joint effusion (7.2%). The incidences of TEAEs with these most common preferred terms were similar between the Gel-One® and PBS treatment groups.

Table 8. Most Frequent (>5% of Subjects in Either Treatment Group) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Name	**PBS (N = 410) n (%)**	**Gel-One® (N = 404) n (%)**	**All Treatments (N = 814) n (%)**
Musculoskeletal and connective tissue disorders	107 (26.1)	108 (26.7)	215 (26.4)
Arthralgia	42 (10.2)	44 (10.9)	86 (10.6)
Joint swelling	42 (10.2)	33 (8.2)	75 (9.2)
Joint effusion	29 (7.1)	30 (7.4)	59 (7.2)

Table 9 below summarizes the treatment-related TEAEs, or adverse device effects, reported in the safety population. Overall, TEAEs in 52 (6.4%) of subjects were considered by the investigator to be related to study treatment. The majority of these subjects (40 subjects; 4.9%) were in the musculoskeletal and connective tissue disorders system organ class. Treatment-emergent adverse events judged to be related to Gel-One® were arthralgia (3.2%), joint swelling (1.7%), joint effusion (1.0%), joint crepitation (0.2%), joint stiffness (0.2%), injection site joint pain (1.0%), injection site joint swelling (0.5%), injection site joint effusion (0.2%), oedema peripheral (0.2%), and urticaria (0.2%). The incidences of adverse device effects were similar in the Gel-One® and PBS groups (6.2% and 6.6% of subjects, respectively).

Table 9. Incidence of Treatment-Related Adverse Events by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Name	**PBS (N = 410) n (%)**	**Gel-One® (N = 404) n (%)**	**All Treatments (N = 814) n (%)**
Musculoskeletal and connective tissue disorders	18 (4.4)	22 (5.4)	40 (4.9)
Arthralgia	10 (2.4)	13 (3.2)	23 (2.8)
Joint swelling	6 (1.5)	7 (1.7)	13 (1.6)
Joint effusion	4 (1.0)	4 (1.0)	8 (1.0)

Joint crepitation	0 (0.0)	1 (0.2)	1 (0.1)
Joint stiffness	2 (0.5)	1 (0.2)	3 (0.4)
Arthropathy	1 (0.2)	0 (0.0)	1 (0.1)
Joint range of motion decreased	1 (0.2)	0 (0.0)	1 (0.1)
Osteoarthritis	1 (0.2)	0 (0.0)	1 (0.1)
General disorders and administration site conditions	8 (2.0)	6 (1.5)	14 (1.7)
Injection site joint pain	6 (1.5)	4 (1.0)	10 (1.2)
Injection site joint swelling	0 (0.0)	2 (0.5)	2 (0.2)
Injection site joint effusion	1 (0.2)	1 (0.2)	2 (0.2)
Oedema peripheral	0 (0.0)	1 (0.2)	1 (0.1)
Injection site joint redness	1 (0.2)	0 (0.0)	1 (0.1)
Injection site pruritus	1 (0.2)	0 (0.0)	1 (0.1)
Skin and subcutaneous tissue disorders	2 (0.5)	1 (0.2)	3 (0.4)
Urticaria	0 (0.0)	1 (0.2)	1 (0.1)
Erythema	1 (0.2)	0 (0.0)	1 (0.1)
Pruritus generalized	1 (0.2)	0 (0.0)	1 (0.1)
Nervous system disorders	1 (0.2)	0 (0.0)	1 (0.1)
Presyncope	1 (0.2)	0 (0.0)	1 (0.1)

2. Effectiveness Results

Primary Effectiveness Endpoint

The analysis of effectiveness was based on the ITT population of 809 subjects (99.0% of randomized subjects) who received the study injection and had data from at least one post-injection visit. The primary effectiveness objective was tested using the null hypothesis that there was no difference between Gel-One® and PBS in the mean change from baseline in pain scores measured following a 50-foot walk test, over 26 weeks. More than a 40% improvement from baseline was demonstrated by the Gel-One® treatment group at all follow-up time points, but, as noted below in Table 10, the treatment group difference in least squares (LS) mean change from baseline over 26 weeks was not statistically significant (P = 0.988).

Table 10. Mean Improvement in VAS Pain Subscore (Following 50-Foot Walk Test) from Baseline at 26 Weeks 50-Foot Walk Test – ITT Population, Gel/1133 Study (N=809)

	PBS (N = 407)		Gel-One® (N = 402)			P-value
	Actual	Change from Baseline	Actual	Change from Baseline	Difference 95% CI	0.988
Baseline	69.36 (SD=7.82)		69.25 (SD=7.64)			

LS mean		-31.7		-31.7	0.0 (-2.7, 2.7)	

Secondary Effectiveness Endpoints

None of the differences between the Gel-One® and PBS treatment groups at 26 weeks were statistically significant for the following secondary endpoints:

- OMERACT-OARSI responder rate
- WOMAC pain subscore
- WOMAC total score
- WOMAC physical function subscore
- WOMAC stiffness subscore
- Physician global evaluation
- Patient global evaluation
- Short Form (36) Health Survey (SF-36) physical component score
- Use of acetaminophen rescue medication

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 38 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.

Post Hoc Non-Inferiority Analysis

A. Non-Inferiority Analysis

A post-hoc non-inferiority analysis was performed by the sponsor to examine the effectiveness of a single injection of Gel-One® relative to three injections of Euflexxa, previously approved under P010029/S008. The Euflexxa FLEXX trial[1] shared many protocol design elements with the Gel-One® protocol (Gel/1133), primarily that the key effectiveness outcome was the pain scores measured following a 50-foot walk test on a 100-mm VAS pain scale and the study follow-up time period was 26 weeks for both protocols for an identical indication for use. The non-inferiority test would assess whether the improvement experienced by the Gel-One® group on a 100-mm VAS scale showed a similar degree of pain relief degree to that reported for the Euflexxa group.

B. Comparison of Gel/1133 Study and FLEXX Trial

The primary effectiveness endpoint and study objective for the indication for use were identical in the Gel/1133 and FLEXX studies. While the dose regimen in each

study differed, with three weekly injections for Euflexxa and a single injection for Gel-One®, the follow-up points after the completion of treatment in the FLEXX trial matched those of the Gel/1133 study. The inclusion/exclusion criteria of the two studies were generally similar. The mean ages and distributions of female and male subjects were similar between the two studies. Subjects in the two studies were limited to only acetaminophen as an analgesic rescue medication during the study. These similarities in the two studies served to justify comparison of the two data sets under a non-inferiority analysis.

C. Data Analyzed

The mean and standard error were calculated for the change from baseline in the pain scores following the 50-foot walk test on the 100-mm VAS for all ITT subjects (n=402) treated with Gel-One® in the Gel/1133 study. The mean and standard error for the change from baseline in the pain scores following the 50-foot walk test on the 100-mm VAS for Euflexxa were obtained from the publication by Altman et al.[1] on the FLEXX trial and were based on the full ITT set (n=291) of subjects treated with Euflexxa in the this trial.

D. Non-Inferiority Analysis Methodology

The Gel/1133 and the FLEXX studies shared nearly identical analyses of their primary outcome. Both modeled the change from baseline in VAS pain scores following the 50-foot walk test in a repeated measures mixed model across time points including Weeks 3, 6, 12, 18, and 26 with fixed effects for visit, treatment, a visit-by-treatment interaction, and a baseline covariate; thus, the estimated change from baseline from the two models share a consistent interpretation. Under the assumption two samples are independent, the standard error of the difference between the two estimates was estimated as $\sqrt{}(SE1^2+SE2^2)$, where SE1 and SE2 are the standard errors of the two estimates.

A non-inferiority margin of 5 mm (on the 100-mm VAS pain scale) was chosen by the sponsor for this analysis based on publically available SSEDs for two recently approved viscosupplement devices, Monovisc (P090031) and Hymovis (P150010).

The analysis tested the null hypothesis that the change from baseline in the VAS pain scores following the 50-foot walk test at Week 26 in the Gel-One® arm in Gel/1133 (δ_{GelOne}) was within 5 mm (or better) than the reported change from baseline for the Euflexxa arm for the FLEXX trial ($\delta_{Euflexxa}$).

This null hypothesis can be expressed as the hypothesis test:

H0: $\delta_{GelOne} - \delta_{Euflexxa} > 5$ vs. HA: $\delta_{GelOne} - \delta_{Euflexxa} \leq 5$

E. Non-Inferiority Analysis Results

The results of this non-inferiority analysis of Gel-One® and Euflexxa are shown below in Table 11.

Table 11. Non-Inferiority Comparison of Mean Changes in VAS Pain Score (Following 50-Foot Walk Test) from Baseline at 26 Weeks between Gel-One® and Euflexxa

Outcome at 26 Weeks	**Euflexxa**	**Gel-One®**
Change from baseline (95% CI)	-25.7 (-29.0, -22.4)	-29.5 (-32.1, -26.9)
Difference (95% CI)*	-3.8 (-inf, -0.3)	

* Gel-One® estimate minus Euflexxa's estimate. Standard Error (SE) is estimated as $\sqrt{(SE1^2+SE2^2)}$, where SE1 and SE2 are the standard errors of the two estimates. 95% CI is a one-sided test for non-inferiority.

This post hoc non inferiority analysis demonstrated Gel-One® to be non-inferior to Euflexxa at 26 weeks in pain reduction scores. There was a measure of uncertainty to this analysis due to the fact that this analysis did not incorporate a direct comparison of the differences between the viscosupplement treatment groups and their respective placebo treatment groups.

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

For all primary and secondary effectiveness endpoints analyzed over 26 weeks in the Gel/1133 study, no statistically significant differences between Gel-One® and the PBS treatment groups were demonstrated.

A post hoc non-inferiority analysis was conducted of Gel-One® and Euflexxa, relying upon a comparison of mean changes from baseline in pain scores measured following a 50-foot walk test, over 26 weeks, the same primary effectiveness endpoint used in the Gel/1133 study. This analysis demonstrated the non-inferiority of Gel-One® to Euflexxa utilizing a non-inferiority margin of 5 mm on a 100-mm VAS pain scale and thereby provided reasonable assurance of the effectiveness of Gel-One® over 26 weeks.

B. Safety Conclusions

The risks of the device are based on data collected in a 26-week pivotal clinical study, Study Gel/1133, conducted to support PMA approval as described above, as well as

data collected in a previous pivotal 13-week clinical trial, Study SI-6606/01, conducted in support of the PMA approval of Gel-One® under P080020.

In the 26-week pivotal trial, Study Gel/1133, the most commonly reported preferred terms of TEAEs for the Gel-One® treatment group were arthralgia (10.9%), joint swelling (8.2%), and joint effusion (7.4%). The incidences of TEAEs with these most common preferred terms were similar between the Gel-One® and PBS treatment groups. Overall adverse event and adverse device effect rates were also similar between the Gel-One® and PBS treatment groups. The majority of AEs were mild in severity and were judged by the investigator not to be related to Gel-One®. There were no deaths or UADEs reported in Study Gel/1133. Overall, these results provide reasonable assurance of the safety of Gel-One®.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support approval of this PMA supplement as described above.

The primary effectiveness objective of the pivotal clinical study for Gel-One® was to demonstrate a clinically meaningful reduction in pain due to OA of the knee, as measured by the 50-foot walk test, over a 26-week evaluation period in subjects treated with Gel-One® compared with subjects treated with a placebo control, PBS. A mean reduction in pain from baseline of 31.7 mm on the whole 100-mm VAS Pain scale at 26 weeks was achieved for both the Gel-One® and PBS treatment groups in this study. While this mean reduction in pain for Gel-One® was clinically meaningful, it nonetheless was no different from that achieved by the PBS control. Thus, the study did not meet its primary effectiveness endpoint.

The sponsor then chose to instead rely upon a post hoc non-inferiority analysis with another commercially available viscosupplement device, Euflexxa (P010029/S008) in order to demonstrate reasonable assurance of effectiveness. In this post hoc analysis, the effectiveness of one injection of Gel-One® was demonstrated to be non-inferior to that of three injections of Euflexxa up through 26 weeks. The mean pain reduction from baseline of one injection of Gel-One® was 29.5 mm at 26 weeks on a whole 100-mm VAS Pain scale, whereas the mean pain reduction for three injections of Euflexxa was 25.7 mm. Thus, the study demonstrated that the probability of achieving a similar degree of pain relief up through 26 weeks using Gel-One® was statistically and clinically comparable to that obtained from using a commercially available viscosupplement approved for identical indications for use.

With regard to the risk profile for this device, harmful events for the Gel-One® treatment group in the study were predominantly mild or moderate and transient in nature. No device-related serious adverse events were reported for the Gel-One® treatment group in the Gel/1133 study. 7 of 404 (1.7%) patients in the Gel-One® treatment group experienced non-device-related serious adverse events. The incidences of treatment-related treatment-emergent adverse events (TEAEs) were

similar in the Gel-One® and PBS treatment groups (6.2% and 6.6% of subjects, respectively).

The most commonly reported preferred terms of TEAEs for the Gel-One® treatment group were arthralgia (44 TEAEs; 10.9% of the total 404 subjects in the Gel-One® treatment group), joint swelling (33 TEAEs; 8.2%), and joint effusion (30 TEAEs; 7.4%).

Treatment-related TEAEs, or adverse events judged to be related to Gel-One® treatment, were arthralgia (13 TEAEs; 3.2% of the total 404 subjects in the Gel-One® treatment group), joint swelling (7 TEAEs; 1.7%), joint effusion (4 TEAEs; 1.0%), joint crepitation (1TEAE; 0.2%), joint stiffness (1 TEAE; 0.2%), injection site joint pain (4 TEAEs; 1.0%), injection site joint swelling (2 TEAEs; 0.5%), injection site joint effusion (1 TEAE; 0.2%), oedema peripheral (1 TEAE; 0.2%), and urticaria (1 TEAE; 0.2%). The incidences of treatment-related TEAEs were similar in the Gel-One® and PBS groups (6.2% and 6.6% of subjects, respectively).

These generally mild or moderate and transient adverse events are accepted and well tolerated by patients given the probable benefits of these devices for providing relief of pain due to osteoarthritis of the knee.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for the indication for use for the treatment of pain in OA of the knee in patients who have failed to respond adequately to non-pharmacologic therapy, NSAIDs or 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.

With regard to the effectiveness of the device, data from the clinical study and a subsequent non-inferiority analysis demonstrated that the probability of achieving a similar degree of pain relief up through 26 weeks using Gel-One® was statistically and clinically comparable to that obtained from using a commercially available viscosupplement approved for identical indications for use.

With regard to the safety of the device, harmful events for the Gel-One® treatment group in the study were predominantly mild or moderate and transient in nature. No device-related serious adverse events were reported for the Gel-One® treatment group in the study. The incidences of TEAEs were similar in the Gel-One® and the PBS

treatment groups, 6.2% and 6.6% of subjects, respectively. The most commonly reported preferred terms of TEAEs for the Gel-One® treatment group were arthralgia (44 TEAEs; 10.9% of the total 404 subjects in the Gel-One® treatment group), joint swelling (33 TEAEs; 8.2%), and joint effusion (30 TEAEs; 7.4%). The probability of the occurrence of such adverse events, given that they were generally transient and mild or moderate in severity, is outweighed by the benefit of extended, clinically significant relief of pain due to OA of the knee achieved for patients in this study.

XIII. CDRH DECISION

CDRH issued an approval order on September 27, 2016.

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.

XV. REFERENCES

1. Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A Double-Blind, Randomized, Saline-Controlled Study of the Efficacy and Safety of EUFLEXXA® for Treatment of Painful Osteoarthritis of the Knee, With an Open-Label Safety Extension (The FLEXX Trial). Semin Arthritis Rheum 2009. 39(1):1-9.