SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Hyaluronic acid

Device Trade Name: Gel-One®

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
Date of FDA Notice of Approval:	March 22, 2011

Expedited: *"not applicable"*

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

Warnings

- Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because sodium hyaluronate can precipitate in their presence.
- Do not inject Gel-One® intravascularly.

Precautions

- Strict aseptic administration technique must be followed.
- Remove joint effusion, if present, before injecting Gel-One®.
- The safety and effectiveness of the use of Gel-One® in joints other than the knee and for conditions other than osteoarthritis have not been established.
- The safety and effectiveness of the use of Gel-One® concomitantly with other intra-articular injectables have not been established.
- The safety and effectiveness of a repeat treatment cycle of Gel-One® have not been established.
- Use caution when injecting Gel-One® into patients who are allergic to cinnamons, avian proteins, feathers, and/or egg products.
- The safety and effectiveness of Gel-One® in severely inflamed knee joints have not been established.
- Do not inject Gel-One® extra-articularly or into the synovial tissue and capsule.
- STERILE CONTENTS. The pre-filled syringe is intended for single use. The contents of the syringe must be used immediately once the container is opened. Discard any unused Gel-One®.

- Do not use Gel-One® if the blister package has been opened or damaged, or if there are cracks or breakage in the pre-filled syringe. Store in the original package below 77ºF (25ºC). DO NOT FREEZE. Do not use after expiration date indicated on package.

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. In Gel-One®, strands of hyaluronan are bound to each other via dimers of cinnamic acid resulting in increased viscoelasticity.
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 A-PET film blister with a Tyvek® lid.

Each pre-filled syringe with 3 mL of Gel-One® contains:
Cross-linked hyarulonate 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 qs. to 3mL
Each package contains 1 blister packed syringes and product information (a package insert).

Shelf life is 12 months.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative Practices and Procedures

For patients who have failed to respond adequately to non-pharmacological therapy, NSAIDs or analgesics (e.g., acetaminophen), alternative practices and procedures include removal of excess fluid from the knee followed by intra-articular 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 treat.

VII. MARKETING HISTORY

Gel-One® has not been marketed in any countries. In 1987, SEIKAGAKU CORPORATION (SKK) launched a sodium hyaluronate product named ARTZ® in Japan, effective for the treatment of OA for the first time in the world. This product was approved with the name of SUPARTZ® in 2001 by FDA (PMA P980044). SKK has developed a new sterile, viscoelastic gel known as Gel-One®, for the same indication for a single injection.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The most common adverse events considered to be related to Gel-One® injection were joint swelling, joint effusion and arthralgia. The adverse events were described in section of the summary of primary clinical study (Section X).

IX. SUMMARY OF PRECLINICAL STUDIES

1. Cytotoxicity:

The potential cytotoxicity of Gel-One® was investigated by the colony assay using L929 cells derived from mouse connective tissue (NCTC clone 929). This study was conducted in compliance with the Japanese GLP (Good Laboratory Practice), the FDA GLP, the International Organization for Standardization(ISO) 10993-5, and the Japanese Biological Safety Test Guideline (Ministry of Health, Labor and Welfare [MHLW] Notification No.0213001: 2003.02.13).

One gram of Gel-One® was extracted with 10 mL of culture medium at 37°C for 24 hours. In the presence of different concentrations (3.13, 6.25, 12.5,25,50 and 100%) of the Gel-One® extracts, the test cells were incubated for 7 days, and all colonies consisting of 50 cells or more were counted in each plate. The colony formation rate in each concentration of Gel-One® extract was comparable with that in the control (concentration: 0%) or that in the extract of negative standard reference material (high-density polyethylene film). No evidence of cytotoxicity was detected under the test conditions.

2. Implantation

The short-term muscle implantation study of Gel-One® was conducted using rabbits. This study was conducted in compliance with the Japanese GLP, the FDA GLP, and the ISO 10993-6.
Gel-One® filled in a polyethylene tube was implanted in the paravertebral muscles of rabbits.
On Days 7 and 28 after implantation, muscle tissue containing the implant specimens was removed and examined macroscopically and histologically. The macroscopic and histological findings of the implant sites of Gel-One® specimens were comparable with those of negative control specimens (polyethylene tube). The average thickness of inflammatory layers around the Gel-One® specimens on Days 7 and 28 were 90 to 146 /lm and 68 to 86 /lm respectively, which were also comparable to those of the negative control specimens (l08 to 155 /lm and 45 to 88 /lm on Days 7 and 28, respectively). From these results, it was concluded that Gel-One® had no adverse effects on the soft tissues (muscles) under the test conditions.

3. Hemocompatibility

The potential hemolytic effect of Gel-One® was investigated using rabbit blood. This study was conducted in compliance with the Japanese GLP and the FDA GLP, and the test methods were referred to the ISO 10993-4 and the ASTM F756-00. Gel-One® was extracted with physiological saline at 37±1°C for 72±2 hrs. To the 3.5 mL of the extract, 0.5 mL of diluted blood at a known concentration of hemoglobin was added, and the mixture was incubated at 37°C for 1, 2 and 4 hours. Then, the concentration of hemoglobin in the supernatant of the mixture was measured by the cyanmethemoglobin method. The hemolytic indices of all the test solutions of Gel-One® were 2% or less at each incubation time, and the grade of hemolysis was assigned as non-hemolytic.

4. Sensitization Test

The skin sensitization potential of Gel-One® was investigated by the Maximization Test using guinea pigs. This study was conducted in compliance with the Japanese GLP, the FDA GLP, and the ISO 10993-10.
Following the intradermal and epidermal induction phases, challenge patch of 0.1 mL of Gel-One® was applied on the skin in the flank region under an occlusive dressing for 24 hours. The challenge patch was removed and the challenge site was observed macroscopically at 24 and 48 hours after the removal. Gel-One® did not induce any skin reaction at either observation point, and it was concluded that Gel-One® had no potential to induce skin sensitization in guinea pigs under the test conditions.

5. Immunogenicity Test

The potential antigenicity of Gel-One® was investigated in the two guinea pig studies. These studies were conducted in compliance with the Japanese GLP, the FDA GLP, and the Immunotoxicity Testing Guidance (CDRH/FDA, 1999). In the first study, guinea pigs (6 animals/group) were subcutaneously sensitized with 200 mg/kg of Gel-One® with or without complete Freund's adjuvant (CFA) once per week for 3 weeks. Fourteen days after the final sensitization, 200 mg/kg of Gel-One® was injected intravenously in order to attempt to elicit an active systemic anaphylaxis reaction. The sera from the sensitized animals obtained 3 days before challenge in the active systemic anaphylaxis test were used to determine the presence of specific antibodies against Gel-One® using passive cutaneous anaphylaxis test. In the Gel-One® group, active systemic anaphylaxis responses were not observed in any of the animals after the challenge with Gel-One®. The passive cutaneous anaphylaxis test revealed no evidence for the

presence of specific antibodies in the sera of the group. In the Gel-One® + CFA group, active systemic anaphylaxis responses were not observed in 5 of 6 animals after the challenge with Gel-One®. The remaining 1 animal exhibited sudden death 22 minutes after challenge. However, the passive cutaneous anaphylaxis test revealed no evidence for presence of specific antibodies in the sera of the group. From these results, the death of the animal was believed due to acute embolization related to the bolus injection of highly viscous Gel-One® solution rather than to an immune-mediated reaction. Although the rate of intravenous injection was not prescribed in this test, the elicitation injection was conducted with a frequently used injection rate (approximately 0.1 mL/sec). The second study was conducted with test methods that were similar to the first study, using 12 guinea pigs in each test group. The intravenous challenges in the active systemic anaphylaxis and the passive cutaneous anaphylaxis tests were conducted at the rate of 1.0 mL/min to avoid embolization. In both the Gel-One® group and the Gel-One® + CFA group, active systemic anaphylaxis responses were not observed in any of the animals after the challenge with Gel-One®. The passive cutaneous anaphylaxis test revealed no evidence for specific antibodies in the sera of sensitized animals. From these results, it was concluded that Gel-One® had minimal potential antigenicity in guinea pigs.

6. Irritation (Intra-Articular)

The potential local irritation of Gel-One® was investigated following a single administration (0.05 mL/kg/joint) into the joint cavity of the rabbit knee. This study was conducted in compliance with the Japanese GLP, the FDA GLP, and the ISO 10993-10. Physiological saline (Japanese pharmacopoeia physiological saline) was used as the negative control material, and SYNVISC® (Hylan G-F 20, Genzyme Biosurgery) was used as the reference control material. On Days 1, 3, 7 and 14 after injection, the number of cells in knee joint lavage fluid was counted, and the knee joint tissues were collected and examined macroscopically and histologically.

At the Gel-One® injection sites, there were no significant increases in knee joint lavage fluid cell counts at any time point, compared to those of physiological saline. Macroscopic and histological examination of the knee joint tissues revealed no abnormalities. Although irritative changes were not observed at the Hylan G-F 20 injection sites in the knee joints collected on Days 1,3 and 7 after injection, knee joint lavage fluid cell counts increased significantly on Day 14 after injection. Histological examination on Day 14 revealed focal inflammatory cell infiltration in the synovial membrane in 1 of 4 joints. From these results, it was concluded that Gel-One® was not irritative in rabbits, and the effect of single intra-articular administration of Gel-One® on the knee joint tissues was comparable to that of physiological saline. The repeated intra-articular administration test of Gel-One® was conducted using beagle dogs. This study was conducted as a non-GLP test, and the purposes of the study were to investigate preliminarily the local and systemic tolerability to Gel-One® and to select the frequency of repeated administration in the 26-week repeated dose toxicity study. In this test, 0.05 mL/kg joint of Gel-One® was repeatedly administered to the bilateral knee joints at an interval of one or two weeks for a total period of 4 weeks or 13 weeks. Three groups were used in the test; a "control group" in which physiological saline was injected once a week, "Gel-One® (1 W) group" in which Gel-One® was injected once a week and "Gel-One® (2W) group" in which Gel-One® was injected every two weeks. Three animals/group were assigned for each administration period (4 weeks and 13 weeks), and a total of 18 animals were used. During the 4-week (injected four times or twice) and 13-week (injected 13 times or 7 times) administration periods, general appearance was observed and body weight and food consumption were measured. On the day after the end of each administration period, animals were euthanatized and their knee joints were removed. The number of cells in knee joint lavage fluid was counted, and the knee joint tissues were examined macroscopical1y and histologically. During the 4-week and 13-week administration periods, no abnormalities were observed in general appearance in any of the test groups. There were no abnormalities in body weight changes and food consumption during these periods. At the end of these administration periods, no statistically significant differences in knee joint lavage fluid cell counts were observed in the Gel-One® groups as compared to those in the control group. Macroscopic observation of the knee joint tissues revealed no abnormalities in any of the test groups. Histological

examination at the end of 4-week administration revealed slight proliferation of synovial1ining cells and slight atrophy of synovial adipose tissue in the synovial membrane in both Gel-One® groups. At the end of 13-week administration, these changes increased in some incidences or degrees, and fibrosis of subsynovial connective tissue was also observed. The incidence and degree of the changes were believed to be related to an increase in the number of injections of Gel-One®. These results were considered to be attributable to the physical effects of repeated administration of the semi-solid material and not to be indicative of tissue-irritability of Gel-One® in itself. From these results, it was concluded that weekly or biweekly intra-articular administration of Gel-One® for 4 or 13 weeks in beagle dogs was wel1 tolerated and the irritative effect of Gel-One® on the knee joint tissues was comparable to that of physiological saline. Repeated administration of Gel-One® into the joint cavity of the knee at frequent intervals may also affect synovial membrane to some extent.

7. Intracutaneous Reactivity

The effect of Gel-One® on the dermal tissues fol1owing intracutaneous injection was investigated using rabbits. This study was conducted in compliance with the Japanese GLP, the FDA GLP, and the ISO 10993-10. To the test animals (12 females), 0.2 mL/site of Gel-One® was injected at 5 sites on the right side of the back, and 0.2 mL/site of physiological saline was injected similarly on the left side. On Days 3, 7, 14 and 28 after injections, the dorsal skins of 3 animals were removed for histological evaluation. The injection sites were macroscopical1y observed from the day after injection to each day of removal. At the Gel-One® injection sites, "upheaval of the injection site (5 mm or less)" accompanied by "very slight erythema" was macroscopical1y observed in all the test animals. The changes gradually decreased, and disappeared by Day 16 after injection. No other abnormal changes were observed at these sites for up to 28 days. Histologically, residual test material was observed at the injection sites in all the animals. The residual quantity of Gel-One® decreased with time, and no other histological abnormalities were observed at these sites. Accordingly, macroscopic changes observed at the injection sites were considered to be attributable to the physical effects of Gel-One®, and not indicative of irritability of Gel-One® itself on the tissues. From these results, it was concluded that Gel-One® did not affect the dermal tissues under the test conditions.

8. Studies on Local Effects of Gel-One®D (degraded Gel-One®)

These studies were conducted to investigate local effects in the case that extremely degraded Gel-One® was injected. Gel-One®D is a sample of Gel-One® with reduced viscosity. It was prepared by heat treatment of Gel-One® at 60°C for 6 days, and the viscosities of Gel-One®D and Gel-One® were 4 Pa-s and 17 Pa-s, respectively. The effect of Gel-One®D and Gel-One® on local tissue was compared by the following studies.

Single Dose Intra-Articular Administration Test

Gel-One®D was investigated for its irritation potential following a single administration (0.05 mL/kg/joint) into the joint cavity of the rabbit knee. Physiological saline (Japanese pharmacopoeia physiological saline) was used as the negative control material, and Gel-One® was used as the reference control material. On Days 1, 3, 7 and 14 after injection, the number of cells in the knee joint lavage fluid was counted, and the knee joint tissues were collected and examined macroscopically and histologically. In the knees treated with Gel-One®D, there was a significant increase in the knee joint lavage fluid cell counts on Day 1. In the macroscopic or histological examination of the knee joint tissues that showed an increase in the knee joint lavage fluid cell counts, however, no abnormalities were observed. Therefore, it was considered that the increase in cell counts was not indicative of irritability of Gel-One®D. Histological examination of synovial tissues from knees treated with Gel-One®D revealed slight proliferation of synovial cells in the synovial membranes in 2 of the 4 knees removed on Day 7. The change was observed also in 1 each of the 4 knees removed on Day 3 and on Day 7 after injection of physiological saline (negative control material); therefore, the change was not considered to be indicative of irritability of Gel-One®D. In the knees treated with Gel-One®, the knee joint lavage fluid cell counts

were comparable to those in the knees treated with physiological saline, with no significant differences. Histological examination of the knee synovial tissues revealed slight proliferation of synovial cells in the synovial membranes in 1/4,2/4, and 1/4 of the sampled 4 knees removed on Days 1,3 and 14, respectively. The degree of these changes was comparable to those observed in the knees treated with physiological saline. In the synovial membrane removed on Day 1, slight hemorrhage in the sub-lining layer was observed in I of the 4 knees. This was assumed to be a secondary change associated with insertion of an injection needle because this was observed in the sub-lining layer and no changes indicative of irritability of Gel-One® was observed in the synovial lining cells. From these results, it was concluded that Gel-One®D was not irritative and the effect of intraarticular injection of Gel-One®D on the knee joint tissues was comparable to that of physiological saline and Gel-One®.

Intracutaneous Reactivity Test

The effect of Gel-One®D on the dermal tissues following intracutaneous administration was investigated in rabbits. Physiological saline was used as the negative control material, and Gel-One® was used as the reference control material. Four test groups (a total of 12 animals, 3 animals/group) were applied, and dorsal skins of animals in each group were removed on respective Days 3, 7, 14 and 28 after the intracutaneous injections. To all of the 12 animals, 0.2 mL/site of Gel-One®D, physiological saline and Gel-One® were injected intracutaneously at 4 sites/material in the dorsal region. The injection sites in all the animals were macroscopically observed daily from Day 1 after injection to the day of removal of the dorsal skin. At the injection sites of Gel-One®D and Gel-One®, "very slight erythema (score 1) " or "upheaval of the injection site (5 mm or less)" was macroscopically observed in all the test groups. These changes gradually decreased, and all of them disappeared by Day 9 after injection of Gel-One®D and by Day 20 after injection of Gel-One® in the group of skin removal on Day 28. Histopathological examination revealed residual test material at the injection sites of Gel-One®D and Gel-One®. There were no changes indicative of irritability in the tissues around the injected materials. The residual quantity decreased with time, and Gel-One®D decreased in a shorter period of time than Gel-One® on and after Day 7. Accordingly, erythema and upheaval observed macroscopically at the injection sites of Gel-OneD and Gel-One® were considered to be attributable to the physical effects of Gel-One®D or Gel-One®, and not indicative of irritability of Gel-One®D or Gel-One® itself on the tissues. From the results, it was concluded that Gel-One®D did not affect the dermal tissues under the test conditions.

9. Systemic Toxicity (Acute)

The acute systemic toxicity of Gel-One® was investigated using mice. This study was conducted in compliance with the Japanese GLP and the FDA GLP, and the test methods were referred to the ISO 10993-11 and the USP 27. A single dose of Gel-One® or the physiological saline extract of Gel-One® was intra-peritoneally administered to 5 mice/group at a volume of 50 mL/kg. After the administration, animals were observed for general appearance and weighed every day, then autopsied on Day 3 after administration. There were no toxic changes after the administration of Gel-One® or Gel-One® extract in general appearance and body weights. Autopsy revealed that there were no treatment related changes indicating toxicity. From these results, it was determined that Gel-One® had minimal potential to induce acute systemic toxicity under the test conditions.

10. Repeated Dose Toxicity (4 Weeks)

Gel-One® was subcutaneously administered at doses of 2, 4 and 8 g (mL)/kg to rats once a week for 4 weeks to evaluate potential toxicity. Recovery following 4-week withdrawal was also investigated. This study was conducted in compliance with the Japanese GLP and the FDA GLP, and the test methods were referred to the ISO 10993-11 and the Organization for Economic Co-operation and Development (OECD) Guideline 407. There were no changes related to the administration of Gel-One® in general appearance, body weight, food consumption, ophthalmology, urinalysis, hematology, blood chemistry, organ weights and histopathological examinations. Autopsy revealed dose-dependent residual test material at the injection sites (subcutis in the dorsal region) in each Gel-One®-treated group at the end of administration.

Histological examination revealed only infiltration of histiocyte and encapsulated fibrosis, which indicated absorption process of the test material. The residual test material was reduced in quantity 4 weeks after withdrawal. From these results, it was concluded that the no-observed-adverse effect-level (NOAEL) of Gel-One® was 8 g (mL)/kg for males and females under the test conditions.

11. Chronic Toxicity (26 Weeks)

Gel-One® was injected intra-articularly into knees of male and female beagle dogs at a volume of 0.05 mL/kg/joint to investigate its safety. Biweekly repeated intra-articular injections were conducted for 26 weeks, followed by a 4-week recovery period to investigate resolution of any observed toxic effects. This study was conducted in compliance with Japanese GLP, FDA GLP, and ISO 10993-11 requirements. During the treatment period there were no abnormalities in general appearance, including gait, in any males or females in the Gel-One®-treated group. In addition, no abnormalities were observed in any animal during the recovery period. There were no toxic changes related to repeated administration of Gel-One® in body weight, food consumption, water consumption, ophthalmology, body temperature, respiration rate, electrocardiogram, blood pressure, urinalysis, hematology, blood chemistry, autopsy, organ weight, the number of cells in the knee joint lavage fluid or histopathology. From these results, it was concluded that biweekly intra-articular administration of 0.05 mL/kg/joint of Gel-One® did not induce any toxic adverse effect in male and female beagle dogs under the test conditions.

12. Genotoxicity

The genetic toxicity of Gel-One® was evaluated in the following three bioassays. None of these tests were suggestive of genotoxicity with Gel-One®.

Bacterial Reverse Mutation Test

The potential of Gel-One® to induce genetic mutation was evaluated by the bacterial reverse mutation test using Salmonella typhimurium TAl00, TA1535, TA98 and TA1537 and Escherichia coli WP2uvrA. This study was conducted in compliance with Japanese GLP, FDA GLP, and ISO 10993-3 requirements. The test was conducted by the pre-incubation method at the concentrations of 313,625, 1250, 2500, and 5000 μg / plate, without or with metabolic activation system (S9 mix). The average number of revertant colonies of each tester strain in the Gel-One®-treated groups was less than twice that in negative control groups, with or without metabolic activation. No increases in the number of revertant colonies were observed following incubation with increasing concentrations of test material. Therefore, test results were judged to be negative, and it was concluded that Gel-One® was non-mutagenic in tester strains.

Chromosomal Aberration Test in Cultured Mammalian Cells

The in vitro clastogenic potential of Gel-One® was evaluated using Chinese hamster lung (CHL/IU) cells. This study was conducted in compliance with Japanese GLP, FDA GLP, and ISO 10993-3 requirements. The test was conducted in 3 series: 6 hours treatment with or without metabolic activation (S9 mix), and continuous treatment for 24 hours. The treatment concentrations of Gel-One® were selected to be 1250, 2500 and 5000 μg/mL, based on preliminary test results indicating "no growth inhibition" to be detected in concentrations in cultured cells ranging from 78.1 to 5000 μg/mL. At these concentrations, the incidence of structural and numerical chromosomal aberrations was less than 5% in all test series. Therefore, results were judged negative, and it was concluded that Gel-One® was non-clastogenic in cultured mammalian cells.

In Vivo Single Cell Gel Electrophoresis Assay

The potential of Gel-One® to cause direct damage on DNA was investigated using mice by the in vivo multi-organ alkaline single cell gel electrophoresis (SCG) assay. This study was conducted in compliance with the Japanese GLP and the FDA GLP, and the test methods were referred to the ISO 10993-3 and the report of Tice, et al (2000). A single dose of25, 50 or 100% solution of the physiological saline extract of Gel-One® was administered intraperitoneally to the mice in a dosing volume of 50 mL/kg. At 3 and 24

hours after the administration, the liver, lung, spleen, kidney, ileum and urinary bladder were removed from the animals. The cells from each organ were embedded in agarose gel, and electrophoresis of nuclear DNA of the cells was conducted under alkali condition. The migrations of nuclear DNA (the difference between total length and head length) and the incidences of DNA damage based on classification by morphology of nuclear image were almost equivalent between Gel-One® groups and physiological saline group (negative control) at each time point. From these results, it was concluded that Gel-One® caused no direct damage on DNA in the organs of mice.

13. Pyrogenicity

The potential pyrogenicity of Gel-One® was investigated using rabbits. This study was conducted in compliance with the Japanese GLP and the FDA GLP, the ISO 10993-11 and the USP 27. Gel-One® was extracted with Japanese pharmacopoeia physiological saline at 37 ± 1°C for 72±2 hours, and the extract was injected into the auricular veins of rabbits at a volume of 10 mL/kg. After the administration, body temperature of each animal was periodically (30, 60, 90, 120, 150 and 180 minutes) measured. There was no individual rise of above 0.5°C higher than the control (pre-injection) body temperature, and the total rise in the body temperatures of the three test animals did not exceed l.4°C. The bacterial endotoxin test revealed that the concentration of endotoxins in the Gel-One® extract was < 0.0057 EU/mL. From these results, it was concluded that Gel-One® was non-pyrogenic under the test conditions.

14. Reproductive and Developmental Toxicity

A preliminary study was conducted to find appropriate dose levels of Gel-One® for the reproductive and developmental toxicity study of Gel-One® in rats by single study design. This study was conducted as a non-GLP study. Gel-One® was subcutaneously administered at the doses of 2, 4 and 8 g (mL)/kg once a week to 6 male and 6 female rats; to males for a total of 4 times; before, during and after the mating period; and to females for a total of 7 or 8 times; before mating, during mating and gestation periods and through 7 days of lactation. The only change related to the test material administration was the residual test material in the administration sites in the parental animals. There were no effects of the test material administration on the reproductive ability of parental animals and on the development and growth of the next generation for up to 7 days. On the basis of the preliminary study results, the main GLP study for the reproductive and developmental toxicity was conducted by the single study design using dose levels of Gel-One® at 2,4 and 8 g (mL)/kg. This study was conducted in compliance with the Japanese GLP and the FDA GLP, and the test methods were referred to the ISO 10993-3 and the OECD Guidelines 414 and 415. Gel-One® was subcutaneously administered once a week at the doses of 2, 4 and 8 g (mL)/kg to 20 male and 40 female rats per group. From half of the females (20 females per group), fetuses were removed and observed at the term of pregnancy (cesarean section group), and the other half (20 females per group) was allowed natural delivery (delivery group). Administration period in males was from 2 weeks before the initiation of mating through the mating period to copulation, and to the day before autopsy. Administration period in females in the cesarean section groups was from 2 weeks before the initiation of mating through the mating period to copulation, and in females with successful copulation, to Day 19 of gestation; in females in the delivery groups, from 2 weeks before the initiation of mating through the mating period to copulation, and in females with successful copulation, during gestation period to Day 21 of lactation. Administration times in parental males, parental females in the cesarean section groups and pregnant females in the delivery groups were 9, 5 to 8 and 9 to 11, respectively. Offspring from the delivery groups were observed to sexual maturity. The only change related to the test material administration was the residual test material in the administration sites in the parental animals. It was observed in all males and females in the treatment groups, in volumes that increased in a dose-dependent manner. In any of the examinations of sperm in males, reproduction performance in males and females, pregnancy, delivery or lactation behavior in maternal animals, no changes related to the test material administration were observed. In the fetal observation at the term of pregnancy and observations of physical differentiation, functional examination or reproduction performance, no abnormal changes

related to the test material were observed in males or females in any treatment groups. From these results, it was concluded that the NOAEL of Gel-One® under the test conditions was 8 g (mL)/kg/week for parental animals, embryos, fetuses, and offspring.

15. Carcinogenicity

Chronic toxicity study (26 weeks exposure) with Gel-One® was not associated with toxic effects. Genotoxicity studies of Gel-One® by 3 different bioassays did not reveal any genotoxicity. No abnormalities were found in chromosomal aberration testing in cultured mammalian cells exposed to Gel-One®. In vivo single cell electrophoresis assays showed that exposure to Gel-One® was not associated with any direct DNA damage. Thus no non-clinical evidence that treatment with Gel-One® is carcinogenic has been observed.

Other Laboratory

Pharmacokinetic Studies

Pharmacokinetic studies in rats after single subcutaneous administration of ^{14}C-labeled Gel-One® showed the following results: The radioactivity uptake into plasma was rapid (1 day), which remained relatively constant for two weeks. The maximum plasma concentrations (Cmax) occurred at 7 days post-injection in males, and 9 days in females. The predominant excretion route was renal. The elimination half-lives ($t_{1/2}$) were 15 days in males and 21 days in females. A bio distribution study in male rats showed detectable levels in the liver, urinary bladder, bone marrow, kidney, spleen and blood. It was expected that blood and tissue concentrations of hyaluronan moiety in Gel-One® after intra-articular injection were below physiological concentrations of hyaluronan.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study *to establish* the safety and effectiveness of Gel-One® (investigational device name: Gel-200) single injection for the treatment of pain in osteoarthritis (OA) of the knee was evaluated in a pivotal study for a randomized, multi-center, double-blind, controlled, parallel-group clinical trial conducted in the United States under IDE G060089. 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 study objective was to determine if a single intra-articular injection of Gel-One® is superior to a single injection of phosphate buffered saline (PBS) in subjects with symptomatic osteoarthritis of the knee. The study was designed to accrue approximately 375 subjects, with a 2:1 randomization of Gel-One® to PBS.

This was a multi-center, randomized, double-blind, controlled, parallel-group study to compare the safety and effectiveness of Gel-One® versus PBS in the treatment of symptomatic OA of the knee. After screening (between 1 and 2 weeks prior to the randomization), subjects received a single injection of Gel-One® or PBS control at Week 0. Subjects were instructed to use only those medications they were receiving for pain at screening (and baseline, prior to injection), and not to initiate use of new analgesic or anti-inflammatory agents during protocol participation. Subjects returned for evaluations at Weeks 1, 3, 6, 9, and 13 for assessment of effectiveness and safety. The study was designed to accrue approximately 375 subjects, with a 2:1 randomization of Gel-One® to PBS. A subject had to report Western Ontario and McMaster Universities Osteoarthritis(WOMAC) Visual Analog Scale (VAS) Pain subscores $\geq$ 40 mm (average of 5 questions about pain) in the affected knee and $\leq$ 20 mm in the contralateral knee at the baseline. The study utilized unilateral treatment with Gel-One® or PBS as active and control injections, respectively. Comparisons between Gel-One® and PBS for the reduction of WOMAC Pain score were assessed at 13 weeks using a spline model and confirmed using a longitudinal testing strategy.

Duration of the Study
The study lasted approximately 15 months. The first subject was randomized on 11 September 2006 and the last subject completed the study on 05 December 2007.

Study Population
The 3 study populations were defined.
Intention-to-treat (ITT) population
ITT population includes all randomized subjects who received the study injection and had at least 1 post injection visit.

Per Protocol (PP) population
PP population includes all ITT subjects who:
- were eligible
- received study injection as randomized (e.g., correct syringe number)
- received the full 3.0 mL injection
- had the treatment blind preserved
- had at least 1 post-injection visit– after exclusion of all visits where proscribed medications were administered
- had at least 1 post-injection visit following exclusions of all visits where supplementary alternative knee therapy were received
- underwent no preplanned major surgical procedures influencing the index knee
- experienced no other major protocol deviations (Note: All protocol violations were reviewed prior to database lock and therefore prior to treatment unblinding).

Safety population
Safety population includes all randomized subjects who received the study injection.

The primary and secondary effectiveness endpoints were performed on ITT and PP populations. The safety analysis was performed using Safety population. PP population was defined to exclude the minimum number of subjects and visits to maximize the ability to draw inference on PP population as well.

Clinical Endpoints
The planned statistical analysis is a superiority design (two-sided test with 5% Type I error, which is equivalent to a one-sided test with 2.5% Type I error) to test if a single, IA injection of Gel-One® is superior to a single, IA injection of PBS control using all available data through Week 13. The primary effectiveness analysis of WOMAC pain score is spline modeling. Longitudinal modeling is used as the confirmatory model. Spline modeling assesses the WOMAC VAS Pain subscore using all available data through Week 13. Longitudinal modeling assesses the WOMAC VAS Pain subscore for baseline and for Week 6 through Week 13. In addition, endpoints are compared using a Wilcoxon-Mann-Whitney test and unpaired t-test across visits as supporting analyses.

Effectiveness Analyses
A multistage analysis strategy was deployed as follows:
1. test for superiority (for primary effectiveness endpoint) using a quadratic spline model requiring that the one-sided 97.5% lower bound for the difference between Gel-One® and PBS at Week 13 be > 0 mm using the spline model.
2. perform sequential testing procedures to establish secondary effectiveness endpoint labeling claims, after the primary effectiveness has been met.
3. conduct supportive analyses to confirm consistency of study conclusions using multiple models, site interaction testing, different study populations, and various imputation strategies.

The baseline (average of screening and Week 0 evaluations) was used in the spline modeling analysis.

Secondary Endpoints
In addition, labeling claims were sought in the same manner for the following secondary effectiveness endpoints using the predefined sequential testing order:

1. OMERACT-OARSI Response
2. Total WOMAC VAS score
3. Physician Global Evaluation
4. Subject Global Evaluation
5. SF-36 PCS
6. Acetaminophen consumption
7. WOMAC VAS Stiffness subscore
8. WOMAC VAS Physical Function subscore

Labeling claims are sought for all effectiveness endpoints achieving significance in the stated order until significance is no longer achieved. No p-value adjustment is required since all endpoints are sequentially analyzed in this predefined order. Furthermore, pre-specified supportive analyses were performed

Safety Analyses
The number of subjects, AE (Adverse Event)s, and Abnormal Laboratory Outcomes (ALOs), and the proportion reporting each AE and ALO were summarized. The severity of the AE and causal relationship to study product were summarized by System Organ Class (SOC) and Preferred Term (PT), and by treatment group. The severity of the ALOs was summarized for each ALO category by treatment group. The frequency of TEAEs (Treatment Emergent Adverse Events) that first appear or worsen after treatment and during the study period) were also summarized for the two treatment groups. The subject-level incidence of these outcomes were analyzed using a Fisher Exact test while the event-level incidence were analyzed using a Poisson model (or Wilcoxon test if there was over dispersion in Poisson models). The subject-level incidence and event-level incidence of signs and symptoms prior to injection (pretreatment signs and symptoms) were also summarized. The subject-level proportions (TEAEs, Unanticipated Adverse Device Events (UADEs) [which were by definition serious], most common AEs [defined by >5% overall incidence], and those starting within 24 hours of the injection) were compared between treatments, using a two-sided Fisher Exact test. The number of AEs and ADRs per treatment group, as well as AEs and ADRs of specific types, were analyzed using a Poisson model (or a Wilcoxon-Mann-Whitney test in case of over dispersion).
The incidence of abnormal examination results of the injected knee (for observation of swelling, redness, or effusion) were displayed overall and at each evaluation. A two-sided Fisher Exact test was used to compare subject-level events while a Poisson model was used to compare the total number of events after accounting for censoring due to losses to follow-up or withdrawals (or a Wilcoxon-Mann-Whitney test in case of over-dispersion).

Concomitant medication use was summarized by treatment group.
Wilcoxon-Mann-Whitney signed rank tests were used to assess laboratory test (hematology and serum chemistry) changes from screening to Week 13.

Serious adverse events (including deaths) and withdrawals due to AEs were summarized by treatment group. Narratives and individual Case Report Forms (CRFs) were presented.

Study Hypotheses

WOMAC Pain Spline Modeling

The null hypothesis for the testing of superiority for spline modeling for WOMAC Pain subscore (and other WOMAC endpoints plus Subject and Physician Global Evaluations) was:

H0: $\Delta 2 - \Delta 1 \leq 0$

and the alternative hypothesis was:

HA: $\Delta 2 - \Delta 1 > 0$ (superiority)

where:

$\Delta 1$ = mean change from baseline (scores subtracted from baseline so that a positive change represented improvement) in WOMAC VAS Pain subscore for PBS

$\Delta 2$ = mean change from baseline (scores subtracted from baseline so that a positive change represented improvement) in WOMAC VAS Pain subscore for Gel-One®

Baseline was defined as the average of the screening and Week 0 evaluations. If either evaluation was missing, but not both, the non missing measure was used as the baseline measurement.

OMERACT-OARSI Response Modeling

A subject was considered an OMERACT-OARSI 'responder' if either of the following 2 criteria were met:

(1) his or her reported improvement from baseline in WOMAC VAS Pain subscore or WOMAC VAS Physical Function subscore was at least 50% and the absolute change was at least 20 mm, or

(2) his or her reported improvement from baseline was at least 20% and the absolute change was at least 10 mm for at least 2 of the following 3 measures:
   (a) WOMACVAS Pain subscore,
   (b) WOMAC VAS Physical Function subscore,
   (c) Subject Global Evaluation.

The null hypothesis for the demonstration of superiority was:

H0: $p2 - p1 \leq 0$

and the alternative hypothesis was:

HA: $p2 - p1 > 0$ (superiority)

where:

p1 = the proportion of responders for PBS

p2 = the proportion of responders for Gel-One®

Inclusion Criteria

Each subject had to meet the following criteria to be eligible for the study:

1. Subjects who have given their informed written consent to participate.
2. Male and female subjects between 40 and 80 years of age.
3. Subjects with a diagnosis of painful, symptomatic tibio-femoral OA of the knee defined by:
   -knee pain while standing, walking and/or in motion of at least 4 weeks duration, and
   -evidence of one or more of the following features in an x-ray taken during the previous 3 months: tibio-femoral osteophytes, osteosclerosis of the femoral or tibial endplates, or joint space narrowing (Grade 1-3 on K-L score).
   When patello-femoral OA is also present, only subjects with predominant tibio-femoral disease compared to patello-femoral disease, based on clinical symptoms and radiological findings, are included.

4. Subjects with unilateral or predominantly unilateral symptomatology. Subjects with both screening and Week 0 WOMAC VAS Pain subscore of ≥ 40 mm in the affected knee and ≤ 20 mm in the contralateral knee. Subjects must be fully weight-bearing on the affected knee and not require use of an ambulatory assistive device, such as a crutch or walker.
5. Willingness to discontinue current OA treatment other than non-steroidal anti-inflammatory drugs (NSAIDs), nonprescription and herbal therapies or chondroprotective agents for the study duration, commencing 1 week prior to the injection. This includes any other IA injections, corticosteroids, opiate analgesics, occlusive dressings, physical therapy, or orthopedic technical measures. If subjects are willing to continue current oral OA treatment (i.e., NSAIDs, nonprescription and herbal therapies or chondroprotective agents except controlled-release preparations), doses must have been stable over 4 weeks prior to the baseline visit and must remain stable during protocol participation; a PRN dosing schedule is acceptable.
6. Willingness to discontinue intermittent or as needed (PRN) short-acting, oral analgesic medications such as opiates and acetaminophen within 24 hours prior to each study visit. (Note: Long-acting analgesics (e.g., analgesic patches, methadone, levorphanol) are prohibited at any time in the study).
7. Subjects who are able, in the opinion of the investigator, to adhere to the visit schedule.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. Hospitalized subjects.
2. Subjects with total loss of joint space based on x-ray of the knee (Grade 4 on K-L score), or subjects who are not fully weight-bearing on the affected knee (e.g., require the use of an ambulatory assistive device, such as a crutch or walker).
3. Subjects with inflammatory diseases of the knee other than OA (e.g., rheumatoid arthritis, chronic hemachromatosis, sickle cell anemia, and/or arthropathies of systemic diseases such as chondrocalcinosis, gout, hemophilia, and infectious diseases of the joints).
4. The presence of a severe joint effusion (a tight, distending effusion of the knee), as assessed by the investigator.
5. Gross obesity defined as body mass index (BMI) >35 kg/m2.
6. Severe false alignment of the axis of the knee (i.e., a severe varum or valgum with >12° deformity and/or clinically relevant moderate to severe instability).
7. Clinical manifestations of OA of either hip and/or a joint replacement of the hip on the same side as the affected knee. Joint replacement of the hip on the contralateral side to the affected knee is not exclusionary provided that the subject does not have symptomatic OA of the hip.
8. Surgery on the symptomatic knee within the previous 12 months (including joint replacement), or arthroscopy of the symptomatic knee within 3 months. (Note: Joint replacement of the contralateral knee is permitted provided it was performed ≥ 12 months previously and the subject does not report pain in the contralateral knee by WOMAC pain subscore ≥ 20 mm.)
9. Administration of IA injections into either knee (e.g., corticosteroids, chondroprotective agents) within the past 4 weeks.
10. Modification of current medications or addition of new medications to treat OA of the knee within the preceding 4 weeks (i.e., change in dose or schedule for at least 4 weeks).
11. Regular use of opiate analgesic medication for pain management. The use of long-acting analgesics such as analgesic patches, methadone, and levorphanol is prohibited at any time during the study.
12. Ongoing or previous participation in another clinical trial within the previous 4 weeks.
13. Administration of IA hyaluronate injections for the treatment of OA of either knee within 6 months.
14. Serious systemic diseases (e.g., uncontrolled diabetes, immunodeficiency syndrome); which would preclude accurate evaluation of study treatment (e.g., significant cardiovascular, renal or liver disease, severe anemia, severe thrombocytopenia, malignancy or severe infectious disease with or without fever); baseline (prior to injection) liver function test (LFT) results (i.e., aspartate amino

transferase [AST] or Serum Glutamic Oxaloacetic Transaminase [SGOT] and alanine amino transferase [ALT] or Serum Glutamic Pyruvate Transaminase [SGPT]) >2.5 x Upper Limits of Normal (ULN) per screening laboratory findings; or psychiatric condition or history of substance or alcohol abuse that, in the opinion of the investigator would interfere with protocol treatment and/or assessment of its benefit and/or risk and/or may interfere with participation in the study.

15. Infectious or inflammatory skin diseases in the area of anticipated knee injections.
16. Female subjects who are pregnant or lactating.
17. Male or female subjects of child bearing potential who are not willing to use adequate contraceptive measures to avoid pregnancy. All sexually active subjects must agree to practice an adequate method of birth control during the study.

    Adequate methods of birth control include the following:
    - Hormonal contraception (female subjects), or use of at least one acceptable barrier method.
    - Acceptable barrier methods include the following:
        1. Diaphragm plus a spermicidal agent.
        2. Condoms (male or female) plus a spermicidal agent.
    - Vasectomy, Hysterectomy, Bilateral Tubal Ligation, Intrauterine Device (IUD),and/or Exclusive sexual partner for whom one of the above acceptable methods applies.

    Women who have not menstruated within the past 2 years are considered postmenopausal and do not need to practice birth control.
18. Subjects who have a known history of allergy to sodium hyaluronate products.
19. Subjects with any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.
20. Subjects with contraindications to acetaminophen.
21. Unwillingness to discontinue physical therapy treatments (e.g., heat, ultrasound, knee brace, etc.).

Data Set Analyzed

Three hundred and seventy nine (379) subjects were enrolled and randomized. Subject evaluability was determined according to prospective criteria defined in the protocol and further clarified before database lock and subsequent unblinding of data. The 3 populations defined in the protocol were Safety, ITT, and PP. Figure 1 and Table 2 summarize the evaluable subjects included in each of these protocol populations. Safety population comprised 377 subjects (249 Gel-One® and 128 PBS). Two subjects were excluded from Safety population because they did not receive study injections. ITT population included 375 subjects (247 Gel-One® and 128 PBS subjects). Two subjects were excluded from ITT population because they did not have post-baseline visits. PP population included 344 subjects (229 Gel-One® and 115 PBS subjects) and was defined as an effectiveness subset comprising all subjects who enrolled and had evaluable visits without major protocol violations. Thirty-one (8.3%) of 375 subjects in ITT population were excluded based on major protocol violations that precluded accurate evaluation of effectiveness. A total of 1800 (1186 for Gel-One® and 614 for PBS) post-baseline visits were evaluable for subjects included in ITT population and 1588 (1057 for Gel-One® and 531 for PBS) post-baseline visits were evaluable for subjects included in PP population. Therefore PP population represents 91.7% of subjects and 88.2% of post-baseline visits in ITT population. A summary of post-baseline visits is provided in Table 1.

B. Accountability of PMA Cohort
(Figure 1. Data Sets Analyzed Flow Chart)

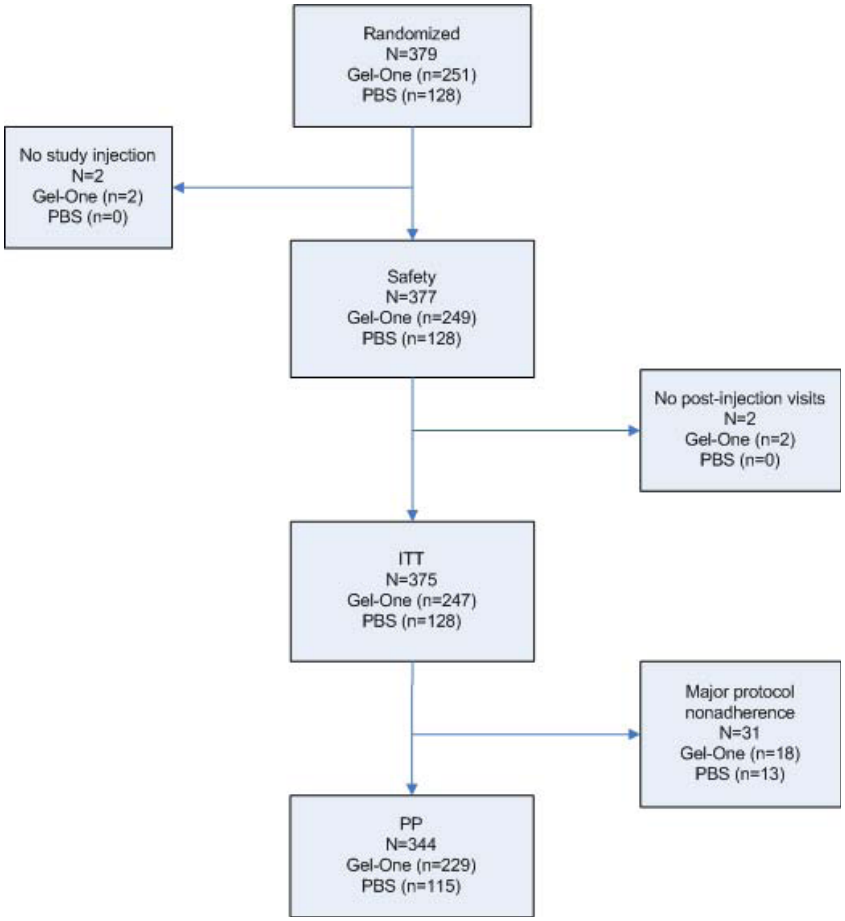

Table 1. Study Visit Counts: ITT and PP Population

	ITT			PP		
	All subjects	Gel-One®	PBS	All subjects	Gel-One®	PBS
Screening	375	247	128	344	229	115
Week 0 (Baseline)	375	247	128	344	229	115
Week 1	374	246	128	329	218	111
Week 3	368	243	125	328	217	111
Week 6	359	235	124	318	211	107
Week 9	349	231	118	307	206	101
Week 13	350	231	119	306	205	101
Total (Post-Baseline)	1800	1186	614	1588	1057	531

Table 2. Subject Evaluability

	All Subjects N (%)	Gel-One® N (%)	PBS N (%)
Number of Subjects Included in Each Population[a]			
Randomized	379 (100.0)	251 (100.0)	128 (100.0)
Safety	377 (99.5)	249 (99.2)	128 (100.0)
ITT	375 (98.9)	247 (98.4)	128 (100.0)
PP	344 (90.8)	229 (91.2)	115 (89.8)
Number of Post-baseline Visits			
ITT	1800	1186	614
PP (with % of ITT)	1588 (88.2)	1057 (89.1)	531 (86.5)
Excluded from Safety Population[b]			
Did not receive study injection	2 (0.5)	2 (0.8)	0 (0.0)
Excluded from ITT Population			
Did not have > 1 post-injection visit	2 (0.5)	2 (0.8)	0 (0.0)
Numbers (with reasons) of ITT Subjects Excluded from PP Population[b]			
Violation of eligibility criteria	13 (3.5)	7 (2.8)	6 (4.7)
– Use of analgesic < 24 hours before baseline visit	6 (1.6)	1 (0.4)	5 (3.9)
– Change in baseline treatment < 4 weeks before baseline visit	3 (0.8)	3 (1.2)	0 (0.0)
– Contralateral knee pain score >20 mm	3 (0.8)	2 (0.8)	1 (0.8)
– History of ipsilateral hip replacement	1 (0.3)	1 (0.4)	0 (0.0)
Violation of concomitant medications	4 (1.1)	3 (1.2)	1 (0.8)
– Used proscribed medications throughout the study from	1 (0.3)	1 (0.4)	– 0 (0.0)

screening			
– No post-injection visit prior to use of proscribed medications	3 (0.8)	2 (0.8)	– 1 (0.8)
Treatment blind not maintained	1 (0.3)	1 (0.4)	0 (0.0)
Underwent post-study injection joint aspiration	2 (0.5)	2 (0.8)	0 (0.0)
Visit window deviation for screening period or last visit	5 (1.3)	4 (1.6)	1(0.8).
Investigational product stored at incorrect temperature	2 (0.5)	0 (0.0)	2 (1.6)
Joint Aspiration, if needed, was not performed prior to study injection	7 (1.9)	4 (1.6)	3 (2.3)

[a] Some subjects could have been excluded from an analysis population for more than 1 reason.
[b] Denominator is number of subjects in respective portion of ITT population.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a osteoarthritis of the knee study performed in the U.S.

Patient Demographics and Baseline Characteristics

Demographics

PP population, which represents 91.7% of ITT population, had comparable baseline demographic and clinical characteristics. It is fully representative of ITT population. The mean age of the study subjects approximated 60 years in both groups; two-thirds of subjects were between 50 and 70 years old. The predominant race was white (about 90% for both groups). More women than men were enrolled, but this difference was comparable in both groups (about 60 % women). These demographics are typical of OA populations. The Gel-One® group had a lower percentage of subjects with K-L score of 1 (9.2% vs. 13.0%) and a higher percentage of K-L score of 3 (54.1% vs. 48.7%). A comparison of mean WOMAC Pain levels across K-L scores and between treatments within each K-L score showed that subjects consistently reported similar pain levels across the 3 K-L scores.

Table 3. Demographics and Clinical Characteristics at Screening

	All Subjects (N = 375)	Gel–One® (N = 247)	PBS ((N = 128)	p-value[a]
Age (years)				0.7325
Mean (SD)	60.7 (10.14)	60.9 (10.24)	60.3 (9.97)	
Median	60.0	60.0	60.0	
Min-Max	40.0, 80.0	40.0, 80.0	40.0, 80.0	
Age groups (n [%])				0.8098
40-50 years	56 (14.9)	34 (13.8)	22 (17.2)	
50-60 years	114 (30.4)	77 (31.2)	37 (28.9)	
60-70 years	121 (32.3)	79 (32.0)	42 (32.8)	
70-80 years	84 (22.4)	57 (23.1)	27 (21.1)	
Gender(n [%])				0.8098
Male	151 (40.3)	100 (40.5)	51 (39.8)	
Female	224 (59.7)	147 (59.5)	77 (60.2)	
Ethnicity (n [%])				1.9121
Hispanic or Latino	42 (11.2)	28 (11.3)	14 (10.9)	
Neither	333 (88.8)	219 (88.7)	114 (89.1)	
Race[b] (n [%])				1.0000
White	344 (91.7)	230 (93.1)	114 (89.1)	
Black/African American	19 (5.1)	10 (4.0)	9 (7.0)	
Asian	2 (0.6)	1 (0.4)	1 (0.8)	
American Indian/Alaska native	1(0.3)	1 (0.4)	0 (0.0)	
Other	9 (2.4)	5 (2.0)	4 (3.1)	
Height (cm)				0.9084
Mean (SD)	168.5 (10.72)	168.5 (10.93)	164.4 (10.32)	
Weight (kg)				0.6300
Mean (SD)	81.4 (15.91)	81.2 (16.47)	81.7 (14.83)	
BMI (kg/m^2)				0.6076
Mean (SD)	28.5 (4.04)	28.3 (4.14)	28.7 (3.83)	
K-L Score - Study Knee				0.2509
1	39 (10.4)	21(8.5)	18 (14.1)	
2	141 (37.6)	94 (38.1)	47 (36.7)	
3	195 (52.0)	132 (53.4)	6 3(49.2)	
WOMAC Pain Subscore - Study Knee				0.0183
Mean (SD)	67.8 (14.86)	69.1 (15.16)	65.3 (13.98)	
WOMAC Pain Subscore - Contralateral Knee				0.6914
Mean (SD)	7.4 (5.55)	7.3 (5.52)	7.6 (5.63)	
WOMAC Stiffness Subscore - Study Knee				0.3165
Mean (SD)	69.6 (19.04)	70.3 (18.97)	68.3 (19.19)	
WOMAC Physical Function Subscore - Study Knee				0.2141
Mean (SD)	66.6 (17.58)	67.4 (17.71)	65.0 (17.27)	
Total WOMAC Score - Study Knee				0.1385
Mean (SD)	67.1 (16.04)	68.0 (16.17)	65.4 (15.71)	

[a] Fisher Exact test and Wilcoxon-Mann-Whitney test for the between treatment comparison in categorical and continuous variables, respectively.

[b] Percentages may not add to 100% since a subject may indicate multiple races. The Fisher Exact test p-value calculation compares white vs. nonwhite. Subjects indicating multiple races are considered nonwhite.

There was a general trend for the Gel-One® treatment group to report higher WOMAC scores at screening and Week 0 baseline visits. Treatment groups were significantly imbalanced by WOMAC Pain at screening, but were comparable at Week 0. Spline and longitudinal modeling accounted for these differences by considering the baseline covariate during the model construction process. These results are summarized in Table 4.

Table 4. Patient Baseline Characteristics – ITT Population

Variable		Gel-One® (N=247)	PBS (N=128)
Age (years)	Mean (SD)	60.9 (10.2)	60.3 (10.0)
Gender (n)	Male	100 (40.5%)	51 (39.8%)
	Female	147 (59.5%)	77 (60.2%)
K-L Score – Study Knee (n)	1	21 (8.5%)	18 (14.1%)
	2	94 (38.1%)	47 (36.7%)
	3	132 (53.4%)	63 (49.2%)
Study Knee			
WOMAC Pain Subscore (mm)	Mean (SD)	70.7 (14.4)	68.0 (13.1)
Total WOMAC Score (mm)	Mean (SD)	69.5 (16.0)	67.8 (14.7)
WOMAC Physical Function (mm)	Mean (SD)	68.9 (17.4)	67.6 (15.8)
WOMAC Stiffness (mm)	Mean (SD)	71.6 (17.5)	69.3 (17.3)
Contralateral Knee			
WOMAC Pain Subscore (mm)	Mean (SD)	7.3 (5.5)	7.6 (5.6)

D. Safety and Effectiveness Results

Data Set Analyzed

379 subjects were enrolled and randomized. Safety population comprised 377 subjects (249 Gel-One® and 128 PBS). Two subjects were excluded from Safety population because they did not receive study injections.

SAFETY RESULTS

Adverse Reactions, Complications, Subject Complaints

Brief Summary of Adverse Events

Pretreatment safety information was recorded during the screening period. Treatment Emergent Adverse Event (TEAE)s, defined as events emerging or worsening after the subject received the study injection, were recorded at each visit (Weeks 1, 3, 6, 9 and 13, and Early Termination). Overall and most common TEAEs, Adverse Device Reactions (ADR)s, Adverse Event (AE)s occurring within 24 hours of the study injection, Serious Adverse Event (SAE)s, and Unanticipated Adverse Device Events (UADEs) are presented in the next sections. Note that AEs with unknown or missing information about causal relationship were counted as ADRs.

The overall incidences of TEAEs, ADRs, and anticipated ADRs were comparable between Gel-One® and PBS treatment groups. The incidence of SAEs was higher in the Gel-One® group, but all SAEs were judged as not related to the study injection. No UADEs, pseudosepsis or definite allergic reactions were reported in either group. Differences between treatments are compared using two-sided Fisher Exact test for subject-level outcomes and by Poisson models (or Wilcoxon-Mann-Whitney tests in the event of over-dispersion).

Adverse Events (Pretreatment Adverse Events, Treatment-Emergent Adverse Events and Serious Adverse Events)

In Gel-One® and PBS treatment groups, 17.3% and 14.1% of subjects, respectively, reported pretreatment AEs ($p>0.4$). The subject-based incidences of TEAEs were 69.1% and 63.3 % in the Gel-One® and PBS treatment groups, respectively. The incidences of pretreatment AEs, and TEAEs and SAEs are presented in Table 5. Eight subjects in the Gel-One® experienced 19 SAEs, all of which were judged as not related to study injection. No subjects receiving PBS experienced an SAE.

Table 5. Summary of Pretreatment AEs and TEAEs and SAEs: Safety Population

	All (N=377)		Gel-One® (N=249)		PBS(N=128)		P-value	
	Events	Subject N (%)	Events	Subject N (%)	Events	Subject N (%)	Events[a]	Subject[b]
Pretreatment AEs	79	61 (16.2)	55	43 (17.3)	24	18 (14.1)	0.4717	0.4632
TEAEs	699	253 (67.1)	483	172 (69.1)	216	81 (63.3)	0.0641	0.2976
SAEs	19	8 (2.1)	19	8 (3.2)	0	0 (0.0)	0.0409	0.0553

[a] Wald chi-square p-value from Poisson model (for Pretreatment AEs and TEAEs) or p-value from Wilcoxon- MannWhitney test (for SAEs) if there is a convergence problem with Poisson model.

[b] Two-sided Fisher Exact test for comparison of subject rates between treatments

Device-Related Adverse Events (Adverse Device Reactions (ADR))

A total of 182 ADRs were reported in 100 subjects: 67 (26.9%) in Gel-One® and 33 (25.8%) in PBS groups experienced 124 and 58 ADRs, respectively. In view of the 2 to 1 randomization, this difference was not significant ($p=0.2336$ and $p=0.9021$, for event- and subjects-based incidences, respectively). No serious anticipated ADRs or UADEs were reported in either group.

Table 6. Summary of Device-Related Adverse Events: Safety Population

	All(N=377)		Gel–One® (N=249)		PBS (N=128)		P-value	
	Events	Subject N (%)	Events	Subject N (%)	Events	Subject N (%)	Events[a]	Subject[b]
ADRs	182	100 (26.5)	124	67(26.9)	58	33(25.8)	0.2336	0.9021
Anticipated ADRs	154	89 (23.6)	106	60(24.1)	48	29(22.7)	0.3552	0.7988
Serious Anticipated ADRs	None							
Unanticipated Adverse Device Effect (UADEs)	None							

[a] Wald chi-square p-value from Poisson model

[b] Two-sided Fisher Exact test for comparison of subject event proportions between treatments

Adverse Events Occurring within 24 hours of Study Injection
The overall incidence of TEAEs occurring within the first 24 hours after injection was similar between treatment groups (p=0.1447): 47 (18.9%) and 16 (12.5%) subjects experiencing 57 and 24 events with Gel-One® and PBS, respectively. The incidences of TEAEs, ADRs and anticipated ADRs within 24 hours of study injection in Safety population are presented in Table 7.

The overall incidence of ADRs within the first 24 hours after injection was numerically higher in Gel-One® compared with PBS groups (14.1% and 10.9% of subjects, respectively), but were not statistically significant. In both treatment groups, the most frequent events were arthralgia, joint swelling and joint effusion. A summary of all ADRs occurring within the first 24 hour after injection is presented by System Organ Class (SOC) and Preferred Term (PT) in Table 7.

Table 7. All Treatment Emergent Adverse Events Occurring within 24 Hours of the Injection: Safety Population

	Gel-One® (N=249)		PBS(N=128)		P-value	
	Events N	Subject N (%)	Events N	Subject N (%)	Events[a]	Subject[b]
TEAEs	57	47 (18.9)	24	16 (12.5)	0.3841	0.1447
ADRs	43	35 (14.1)	19	14 (10.9)	0.5527	0.4238
Anticipated ADRs	35	31 (12.4)	16	13 (10.2)	0.6677	0.6122

[a] Wald chi-square p-value from Poisson model
[b] Two-sided Fisher Exact test for comparison of subject rates between treatments

Table 8. Adverse Device Reactions Occurring within 24 Hours of the Injection: Number Observed and Rate by SOC and PT

	Gel–One® (N=249)		PBS (N=128)	
	Events	Subject N (%)	Events	Subject N (%)
Any ADR occurring within 24 h	43	35(14.1)	19	14(10.9)
General disorders and administration site conditions				
Effusion	4	3 (1.2)	1	1(0.8)
Injection site bruising	0	0	1	1(0.8)
Injection site erythema	1	1(0.4)	0	0
Injection site pain	1	1(0.4)	0	0
Injury, poisoning, and procedural complications	2	2 (0.8)	0	0
Contusion	0	0	1	1(0.8)
Musculoskeletal and connective tissue disorders	0	0	1	1(0.8)
Arthralgia	35	30 (12.0)	17	13 (10.2)
Joint effusion	7	7 (2.8)	5	5 (3.9)
Joint stiffness	14	14 (5.6)	4	4 (3.1)
Joint swelling	2	2 (0.8)	1	1 (0.8)
Joint warmth	11	11(4.4)	6	6 (4.7)

Muscular weakness	0	0	1	1(0.8)
Nervous system disorders	1	1(0.4)	0	0
Dizziness	2	2 (0.8)	0	0
Skin and subcutaneous tissue disorders	2	2 (0.8)	0	0
Rash	1	1(0.4)	0	0
Vascular disorders	1	1(0.4)	0	0
Hypertension	1	1(0.4)	0	0
	1	1(0.4)	0	0

Most Common Treatment Emergent Adverse Events and Adverse Device Reactions
The most common TEAEs 5% of all Subjects) involved musculoskeletal or connective tissue disorders with a total of 341 events in 177 subjects and comprised joint swelling, joint effusion, and arthralgia without significant difference in their incidence between treatment groups.
The most common ADRs (> 5% of all Subjects) experienced were also joint swelling, joint effusion, and arthralgia with a total of 143 events in 84 subjects. Incidences of the most commonly reported TEAEs and ADRs are presented in Table 9 and Table 10. Other ADRs included injection site pain (2.0%), joint stiffness (0.8%), muscular weakness (0.8%), dizziness (0.8%), erythema (0.8%), effusion (0.4%), injection site bruising (0.4%), injection site erythema (0.4%), swelling (0.4%), increased alanine aminotransferase (0.4%), increased white blood cell count (0.4%), back pain (0.4%), muscle spasms (0.4%), synovitis (0.4%), tension headache (0.4%), rash (0.4%), rash pruritic (0.4%) and hypertension (0.4%). ADRs are presented in Table 11.

Table 9. Most Common Treatment Emergent Adverse Events (> 5% of all Subjects) Events Observed and Incidence: Safety Population

	Gel-One® (N=249)		PBS (N=128)		P-value	
	Events	Subject N (%)	Events	Subject N (%)	Events[a]	Subject[b]
Any TEAE in .≥ 5% of subjects	231	122 (49.0)	110	55 (43.0)	0.4529	0.2778
Musculoskeletal and connective tissue disorders						
Joint swelling	91	70 (28.1)	42	36 (28.1)	0.5263	1.0000
Joint effusion	69	58 (23.3)	40	33 (25.8)	0.5807	0.6125
Arthralgia	55	44 (17.7)	22	15 (11.7)	0.3003	0.138
Infections and Infestations						
Upper respiratory tract infections	16	16 (6.4)	6	6 (4.7)	0.4961	0.644

[a] Wald chi-square p-value from Poisson model
[b] Two-sided Fisher Exact test for comparing subject rates between treatments

Table10. Most Common Adverse Device Reactions (>5% of all Subjects) Events Observed and Incidence: Safety Population

	Gel-One® (N=249)		PBS (N=128)		P-value	
	Events	Subject N (%)	Events	Subject N (%)	Events[a]	Subject[b]
Joint swelling	43	35 (14.1)	18	15 (11.7)	0.4420	0.6310
Joint effusion	31	28 (11.2)	13	13 (10.2)	0.5171	0.8618
Arthralgia	24	19 (7.6)	14	12 (9.4)	0.7302	0.5579

[a] Wald chi-square p-value from Poisson model
[b] Two-sided Fisher Exact test for comparison of subject rates between treatments

Table 11. Adverse Events Related to Study Treatment

System Organ Class	**Preferred Term**	**Gel-One® (N=249)**	**PBS (N=128)**
Musculoskeletal and connective tissue disorders	Joint swelling (knee)	35 (14.1%)	15 (11.7%)
	Joint effusion (knee)	28 (11.2%)	13 (10.2%)
	Arthralgia (knee/hip)	19 (7.6%)	12 (9.4%)
	Joint stiffness (knee)	2 (0.8%)	1 (0.8%)
	Muscular weakness (knee)	2 (0.8%)	1 (0.8%)
	Back pain	1 (0.4%)	1 (0.8%)
	Joint warmth (knee)	0	1 (0.8%)
	Muscle spasms (knee)	1 (0.4%)	0
	Synovitis (knee)	1 (0.4%)	0
General disorders and administration site conditions	Injection site pain	5 (2.0%)	1 (0.8%)
	Effusion	1 (0.4%)	1 (0.8%)
	Injection site erythema	1 (0.4%)	1 (0.8%)
	Injection site bruising	1 (0.4%)	0
	Swelling	1 (0.4%)	0
Skin and subcutaneous tissue disorders	Erythema	2 (0.8%)	0
	Rash	1 (0.4%)	0
	Rash pruritic	1 (0.4%)	0
Nervous system disorders	Headache	0	2 (1.6%)
	Dizziness	2 (0.8%)	0
	Burning sensation	0	1 (0.8%)
	Tension headache	1 (0.4%)	0
Investigations	Increased alanine aminotransferase	1 (0.4%)	0
	Increased white blood cell count	1 (0.4%)	0
Vascular disorders	Hypertension	1 (0.4%)	0

Ear and labyrinth disorders	Hearing impaired	0	1 (0.8%)
Infections and infestations	Cellulitis	0	1 (0.8%)
Injury, poisoning and procedural complications	Contusion	0	1 (0.8%)

2. Effectiveness Results

The analysis of effectiveness was based on the 375 evaluable at the 6-month timepoint. Key effectiveness outcomes are presented in tables 12 to 14.

Effectiveness Results

The primary effectiveness analysis of WOMAC pain score was spline modeling. Longitudinal modeling was used as the confirmatory model. Spline modeling assesses the WOMAC VAS Pain subscore using all available data through Week 13. Longitudinal modeling assessed the WOMAC VAS Pain subscore for baseline and for Week 6 through Week 13. In addition, endpoints were compared using a Wilcoxon-Mann-Whitney test and unpaired t-test across visits as supporting analyses.

Effectiveness Analyses

A multistage analysis strategy was deployed as follows:

1. test for superiority (for primary effectiveness endpoint) using a quadratic spline model requiring that the one-sided 97.5% lower bound for the difference between Gel-One® and PBS for Week 13 be > 0 mm using the spline model.
2. perform sequential testing to establish secondary effectiveness endpoint labeling claims.
3. conduct supportive analyses to confirm consistency of study conclusions using multiple models, site interaction testing, different study populations, and various imputation strategies.

The baseline (average of screening and Week 0 evaluations) was used in the spline modeling analysis. The analysis of WOMAC VAS Pain Subscore at Week 13 of ITT population (n=375) was analyzed in the spline model using repeated measures of mixed model of analysis covariance. There was a statistically significant difference of 6.39 mm in the means of WOMAC pain reduction (Gel-One® - PBS) between the two groups at 13 week. The difference of 6.39 mm on the whole 100mm WOMAC VAS Pain Subscore is effective.

Figure 2. Improvement from Baseline in WOMAC VAS Pain Subscore at Week 13 – ITT (N=375) Population

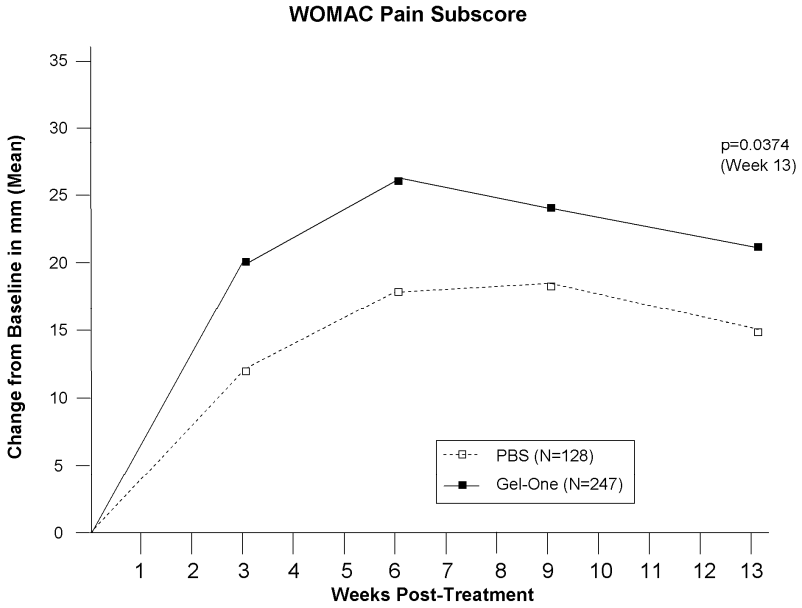

Table 12. WOMAC VAS Pain[a] Improvement from Baseline at 13 weeks (Intent to Treat Population (N=375))

Assessed Time-point	Model-Estimated Advantage (Gel-One® - PBS)	2- sided lower 95%confidence limit (mm)	Two-sided P-value[b]
At Week 13	6.39 mm	0.37	0.0374

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

[b] The analysis is based on the quadratic spline model at knot of 6 weeks at week 13 for the primary endpoint.

The analyses are based on the spline model at week 13 for the primary endpoint.

Secondary Endpoints

In addition, labeling claims were sought in the same manner for the following secondary effectiveness endpoints using the predefined sequential testing order:

1. OMERACT-OARSI Response
2. Total WOMAC VAS score
3. Physician Global Evaluation
4. Subject Global Evaluation
5. SF-36 PCS
6. Acetaminophen consumption

7. WOMAC VAS Stiffness subscore
8. WOMAC VAS Physical Function subscore

Labeling claims were sought for all effectiveness endpoints achieving significance in the stated order until significance was no longer achieved. No p-value adjustment was required since all endpoints were sequentially analyzed in this predefined order.

Summary of Secondary Effectiveness[a] Endpoints at Week 13 – ITT Population

1. OMERACT-OARSI Response
   A subject was considered an OMERACT-OARSI 'responder' if either of the following 2 criteria were met:

(1) his or her reported improvement from baseline in WOMAC VAS Pain subscore or WOMAC VAS Physical Function subscore was at least 50% and the absolute change was at least 20 mm, or

(2) his or her reported improvement from baseline was at least 20% and the absolute change was at least 10 mm for at least 2 of the following 3 measures: (a) WOMAC VAS Pain subscore, (b) WOMAC VAS Physical Function subscore, (c) Subject Global Evaluation.

The OMERACT-OARSI Responses was the first of the secondary endpoints to be tested in sequential testing order. The OMERACT-OARSI Responses was analyzed with generalized estimating equation (GEE), and there was no statistically significant difference with p-value of 0.2418.

Table 13. OMERACT-OARSI Responses[a] – ITT Population
(Intent to Treat Population (N=375))

Odds Ratio[b]	2-sided 95% Lower Bound of Confidence Interval of odds ratio[c]	Two-sided P-value[d]
1.27	0.85	0.2418

[a] subject was considered an OMERACT-OARSI 'responder' if either of the following 2 criteria were met:
(1) his or her reported improvement from baseline in WOMAC VAS Pain subscore or WOMAC VAS Physical Function subscore was at least 50% and the absolute change was at least 20 mm, or
(2) his or her reported improvement from baseline was at least 20% and the absolute change was at least 10 mm for at least 2 of the following 3 measures:

(a) WOMACVAS Pain subscore,
(b) WOMAC VAS Physical Function subscore,
(c) Subject Global Evaluation.

[b] $e^{(\text{Log Odds Ratio})} = 1.27$,.based on GEE model

(Log Odds Ratio)$=\log_e$[probability(responder)/ probability (non-responder)]$_{\text{Gel-One}}$ / [probability (responder)/ probability(non-responder)]$_{\text{PBS}}$

[c] When odds ratio >1, [probability(responder)/ probability (non-responder)$_{\text{Gel-One}}$] > [probability (responder)/ probability (non- responder)$_{\text{PBS}}$] and thus in favor of Gel-One.

[d] Statistically not significant

Other Secondary Endpoints
Total WOMAC Score, WOMAC Stiffness, WOMAC Physical Function were analyzed using the spline model and did not meet the statistical significances. The differences between the two groups at 13 weeks could occur by chance alone.

Table 14. Summary of Other Secondary Effectiveness[a] Endpoints at Week 13 – ITT Population (N=375)

Effectiveness Measures[b]	Model-Estimated Advantage (Gel-One® vs. PBS)	2-sided lower 95% confidence Limit (mm)	Two-sided P-value[c]
Total WOMAC Score	5.64 mm	-0.20	0.0583
WOMAC Stiffness	4.91 mm	-1.31	0.1216
WOMAC Physical Function	5.42 mm	-0.47	0.0714

[a] based on the spline model at week 13.
[b] The WOMAC scale is 100mm.
[c] P- value was not adjusted for the multiplicity of secondary endpoints.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The initial analysis of the primary endpoint did not show a statistical significance at 13 weeks, when the random effect in the spline model using a mixed model of analysis of variance. When the sponsor subsequently excluded the random effect the statistical model, there was a statistical significance at 13 weeks. Our FDA statistician concurred that the sponsor's subsequent analysis is correct. Therefore, the sponsor's analysis of the primary endpoint showed that there was a statistically significant difference between the two groups at 13 weeks in WOMAC VAS Pain Subscore of ITT population (n=375).

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

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

A. Panel Meeting Recommendation

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

B. FDA's Post-Panel Action

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above.
As to the device-related adverse events (ADR: Adverse Device Reactions), a total of 182 ADRs were reported in 100 subjects: 67 (26.9%) in Gel-One® and 33 (25.8%) in PBS groups experienced 124 and 58 ADRs, respectively. In view of the 2 to 1 randomization, this difference was not significant (p=0.2336 and p=0.9021, for event- and subjects-based incidences, respectively). No serious anticipated ADRs or Unanticipated Adverse Device Effects (UADEs) were reported in either group. The ADR is comparable to each other in two groups. The device is reasonably safe.

B. Effectiveness Conclusions

Gel-One® from the SEIKAGAKU CORPORATION, is effective up to 13 weeks, when considering that there was a statistically significant difference with the analysis of WOMAC VAS Pain Subscore at Week 13 of ITT population (n=375) using the spline model with repeated measures of mixed model of analysis covariance. The statistical analysis showed that there was a statistically significant difference of 6.39 mm in the means of WOMAC pain reduction (Gel-One® - PBS) between the two groups at 13 weeks.

C. **Overall Conclusions**

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

This device (Gel-One®) from the SEIKAGAKU CORPORATION, is effective up to 13 weeks, when considering that there was a statistically significant difference with the analysis of WOMAC VAS Pain Subscore at Week 13 of ITT population (n=375) using the spline model with repeated measures of mixed model of analysis covariance. The statistical analysis showed that there was a statistically significant difference of 6.39 mm in the means of WOMAC pain reduction (Gel-One® - PBS) between the two groups at 13 weeks. Concerning the device's safety, the adverse events in the two study groups were comparable to each other. There is no apparent safety issue.

XIV. CDRH DECISION

CDRH issued an approval order on March 22, 2011.

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

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.