FDA SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Sodium Hyaluronate for Injection
Device Trade Name:	Gel-Syn™
Device Procode:	MOZ
Applicant's Name and Address:	Institut Biochimique S.A. (IBSA) Via del Piano - 6915 Pambio-Noranco, Switzerland United States Agent: Clarence Jones, Ph.D. 100 East Thousand Oaks Blvd. Suite 139 Thousand Oaks, CA 91360 (805) 497-2424 (phone/fax)
Date(s) of Panel Recommendation:	not applicable
Premarket Approval Application (PMA) Number:	P110005
Date of FDA Notice of Approval:	May 9, 2014
Expedited:	not applicable

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

- Do not administer to patients with known hypersensitivity (allergy) to sodium hyaluronate preparations.
- Do not inject Gel-Syn into the knees of patients having knee joint infections or skin diseases or infections in the area of the injection site.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the Synovial labeling.

V. DEVICE DESCRIPTION

Gel-Syn is an aqueous solution containing highly purified sodium hyaluronate produced by bacterial fermentation. Sodium hyaluronate is a naturally occurring long-chain polymer of the glycosaminoglycan family consisting of repeating disaccharide units of D-glucuronate-N-acetylglucosamine. The average molecular weight of the hyaluronic acid in Gel-Syn is approximately 1100 kDaltons. Gel-Syn contains 16.8 mg of sodium hyaluronate in 2 mL of physiological sodium chloride solution (0.84%) buffered to a pH of 6.5 to 7.5, and has a dynamic viscosity of >150 mPa.s. It is supplied in a 2.25 mL glass syringe containing 2.1 mL of finished product, with one or three syringes each blister wrapped in the final package. The contents of the syringe are sterile and nonpyrogenic.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

VII. MARKETING HISTORY

Gel-Syn was first approved for commercial distribution in 2002 in two countries in Europe, France and Switzerland. Since then, it has been approved in Italy (2003), Cyprus, Czech Republic, Lebanon, Romania (2004), Libya, Slovakia (2005), Malaysia (2006), and Macedonia (2009), Bosnia Herzegovina, Turkey and Albania (2010), Saudi Arabia and Israel (2011), Germany and Egypt (2012). Gel-Syn has never been withdrawn from any market for which it has been approved.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following adverse events related to Gel-Syn are among those that may occur in association with intra-articular injections: arthralgia, joint stiffness, joint effusion, joint swelling, joint warmth, injection site pain, arthritis, arthropathy, and gait disturbance. According to post-marketing experience of other sodium hyaluronate preparations, anaphylactic/anaphylactoid reactions accompanied by transient hypotension (sudden drop in blood pressure), have been rarely reported worldwide, all of which resolved either spontaneously or after conservative treatment.

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

IX. SUMMARY OF PRECLINICAL STUDIES

Preclinical studies have been performed by both the manufacturer of the sodium hyaluronate (HA) used in the finished product Gel-Syn (HTL S.r.l), as well as the Gel-Syn manufacturer (IBSA Farmaceutici Italia S.r.l). It should be noted that HTL evaluated 2% sodium hyaluronate, while IBSA Farmaceutici Italia tested the finished product which contains a lower concentration of active (0.84%). .

Pyrogen Testing

Testing was performed to assess any potential pyrogenecity in the sodium hyaluronate component of Gel-Syn. Two-percent sodium hyaluronate was diluted 1:4 in physiological saline and injected intravenously into each of three female rabbits at 10 mL/kg. Body temperatures were recorded at 30, 60, 90, 120, 150 and 180 minutes post-injection, with all animals meeting the USP requirement for a negative pyrogen test (temperature increase $<0.5^{o}$C). The result showed that the 2% sodium hyaluronate was not pyrogenic, and therefore the results of the pyrogen testing were negative.

Hemocompatibility

- Fibrinogen Consumption Test

Fibrinogen is an essential plasma protein that can have a greater or lesser affinity for artificial surfaces. A correlation has been established between the adsorption of fibrinogen onto the surface of a biomaterial and the secretion of β-thromboglobulin from platelets, suggesting that the adsorption of fibrinogen is one of the main determinants of the hemocompatibility of biomaterials.

Citrated blood from three human donors was incubated in a 50 mL Falcon tube for one hour at 37^{o}C either alone or in the presence of 2% sodium hyaluronate (0.2 g/mL of blood). At the end of the incubation period, the tubes were centrifuged at 3000 rpm for 10 minutes and the plasma was removed. Plasma fibrinogen levels, assessed using a chronometric technique based on the conversion of fibrinogen to fibrin in the presence of thrombin, were found to be comparable in both the negative control and test samples. The results of the test showed that hyaluronic acid gel does not significantly affect plasma fibrinogen levels after an hour of contact with human whole blood. The result is acceptable.

- Platelet Activation Test

"In vivo" platelet activation markers are substances secreted in plasma by activated platelets: PF4, β_2-thromboglobulin and the metabolites of thromboxane A_2. These markers are widely used in basic research, but there are technical problems with respect to the method of drawing and processing samples.

Platelet-rich plasma from the citrated blood of three human donors was incubated for one hour at 37^{o}C either alone or with sodium hyaluronate at one of two concentrations (0.6 mL of 2% HA/2.4 mL of platelet suspension or 0.3 mL of 2% HA/2.7 mL of platelet suspension), with the incubation time for the positive control (phorbol myristate acetate) being limited to 15 minutes. After incubation and washing, the platelet suspensions were

incubated for 30 minutes at 4°C with a fluorescein isothiocyanate conjugated monoclonal antibody (CD62) which binds to GMP 140 receptors on activated platelets. Following further washing, a flow cytometer was used to assess the degree of fluorescence in each of the samples, a correlate of the quantity of platelet bound CD62 antibody and the extent of platelet activation. No differences in fluorescent intensity were observed for the sodium hyaluronate and negative control samples whose values were approximately one-half the positive control. The result showed that no platelet activation was demonstrated for hyaluronic acid gel (H222G3) by the test for GMP-140 membrane antigen by flow cytometry. The result was acceptable.

- Complement Activation Test

An "in vitro" study of the capacity of the to activate the human complement system in the presence of 2% sodium hyaluronate was conducted by measuring the consumption of complement (CH50) and the production of C3adesArg in serum. Serum was prepared from two human donors and incubated at 37°C either alone, with 2% sodium hyaluronate at one of two concentrations (0.1 and 0.2 g/mL), or zymozan at 2.5 mg/mL (positive control alternate complement pathway activator). Following incubation, the test samples were aliquoted and stored at -80°C until being assayed for total hemolytic complement activity with sheep red blood cells coated with rabbit anti-sheep IgG antibody (CH50), or complement C3a split product (C3adesARG) using a radioimmunoassay. Although CH50 values for the sodium hyaluronate samples in comparison to the negative control indicated an absence of complement activation, C3adesARG levels were somewhat lower in the former, presumably due to the absorption of this cationic peptide onto the sodium hyaluronate molecules which are anionic in nature. The test result showed that hyaluronic acid gel does not activate the complement system, since no significant consumption of CH50 was demonstrated. The result was acceptable.

- Hemolytic Activity Test

Hemolysis test (human blood) under static conditions, performed with an extract (2% sodium hyaluronate), according to ASTM F756-87 "Standard practice for assessment of hemolytic properties of materials" was performed.

Citrated blood was obtained from three human donors and hemoglobin levels were adjusted to 2.50 ± 0.25 mg/mL. Five milliliters of blood were added to 4 mL of an extract of 2% sodium hyaluronate (0.1 g HA/mL 0.9% saline for 120 hr at 37°C), 0.9% saline (negative control) or distilled water (positive control) in 50 mL Falcon tubes which were sealed and placed at 37°C for 4 hours, after which time they were centrifuged and the supernatant was removed and assayed for hemoglobin. An extract of 2% sodium hyaluronate exhibited the same hemolytic properties as the negative control. The result showed that the extraction liquid obtained from hyaluronic acid gel had no more hemolytic activity than the negative control. The result was acceptable.

In Vitro Cytotoxicity

Cytotoxicity test according to ISO 10993-5 (or EN 30993-5) "Biological evaluation of medical devices - Tests for cytotoxicity: in vitro methods" was performed to test the cytotoxicity of the 2% sodium hyaluronate.

- BALB/3T3 Fibroblasts

BALB/3T3 murine embryonic fibroblasts were grown to pre-confluence monolayers in multiwall plates at 37^{o}C for 24 hours, after which the growth medium was withdrawn and replaced with a 120 hour/37^{o}C extract of 2% sodium hyaluronate (undiluted, 1:2, 1:10, 1:100), the extraction vehicle (Modified Dulbecco's Medium) at the same concentrations as the test, a negative control (supplemented Dulbecco's Medium), or a positive control (0.64 mg/mL phenol). The plates were incubated in a humid atmosphere with 5% (v/v) CO_2 for 24 hours, and then the cells were detached with trypsin and left to briefly incubate (2 minutes) in the presence of Trypan Blue before counting the number of dead (blue) or live (unstained) cells with a hemocytometer. The number of viable cells was approximately 2.5 fold greater for each of the dilutions of the 2% sodium hyaluronate extract tested, as well as the extraction vehicle and negative control, in comparison to the cells incubated with the positive control.

In a second study, to assess the direct cytotoxic effect on BALB/3T3 cells, an experiment essentially identical to that described above was completed, except that the test consisted of 100 µL of 2% sodium hyaluronate, with the positive and negative controls remaining the same. Results were similar to sodium hyaluronate extract experiment, with the number of viable cells being approximately 2.7 fold greater for the test and negative control in comparison to the cells incubated with phenol at 0.64 mg/mL. The result showed that the test material, hyaluronic acid gel (batch H 222 G3), supplied by laboratoires SEBBIN is not cytotoxic within the context of ISO standard 10993-5 "Biological evaluation of medical devices -Tests for cytotoxicity: in vitro methods". Hyaluronic acid gel (batch H 222 G3), supplied by laboratoires SEBBIN, is not cytotoxic. The result was acceptable.

- Murine Fibroblasts

A toxicological study, Cytotoxicity by Direct Contact, was conducted on the test sample sodium hyaluronate sterile syringe 16.0 mg/2 mL in order to provide data necessary to the evaluation of biocompatibility.

L-929 murine fibroblasts were grown to confluence on tissue culture plates, to which 100 mm^2 of either Gel-Syn (50 µL/absorbent matrix), USP plastic filament (negative control), or latex (positive control) was applied. Following a 24-hour incubation period at 37°C/ 5% CO2, the plates were examined under an inverted microscope for evidence of cell degeneration/ malformation that was scored on a five-point scale from 0 (no detectable reactivity zone around or under specimen) to 4 (zone extends to more than 1.0 cm beyond specimen). For each of the test samples, which were run in triplicate, scores of 0 were recorded for both the negative control and Gel-Syn, in contrast to 3 for the positive control (i.e. reactivity zone extended 0.5 to 1.0 cm beyond the specimen). The result showed that test substance sodium hyaluronate sterile syringe 16.0 mg/2 mL (Sinovial), is to be considered non-cytotoxic. The result was acceptable.

Genotoxicity

Bacterial Mutation (Ames) Test

The mutagenic activity was determined by comparing the number of revertants in the Test cultures to those in the controls. Such activity was tested both in the presence and absence of metabolic activation. The test sample was used as provided and diluted in sterile deionized water in the following manner: 1:10, 1:100, 1:1000, and 1:10000. One-tenth milliliter of Gel-Syn (undiluted, serial 10^{2-5} dilutions) was added to 2.0 mL of agar, which was kept fluid in sterile test tubes placed in a thermostatic bath at 45°C ± 1°C. Another 0.1 mL of one of five Salmonella typhimurium strains (TA 98, 100, 1535, 1537, 1538), at a concentration of 10^8 to 10^9 cells/mL, was then added along with 0.5 mL of either phosphate buffered saline or S9 mix from aroclor 1254 exposed hepatic homogenate from male rats. Samples were briefly stirred and then poured onto plates containing an agar-containing medium. At the same time, negative and positive (sodium azide, 9-aminoacridine, 2-aminoanthracene, or 2-nitrofluorene) control plates were prepared in replicates of three as per the test samples, and incubated at 37°C ± 1°C for 48-72 hours, at which time revertant colonies were enumerated. Gel-Syn, at the five concentrations tested in two separate studies, was not found to be microbiocidal, nor did any of the concentrations induce an increase (either with or without S9 activation) in revertants in comparison to the negative control for any of the five Salmonella strains employed in the assay. The result showed that the test material, hyaluronic acid gel, is not cytotoxic within the context of ISO standard 10993-5 "Biological evaluation of medical devices - Tests for cytotoxicity: in vitro methods". The result was acceptable.

Acute Toxicity Test

Acute systemic toxicity testing in the mouse following intravenous injection of the extraction liquid from a biomaterial was performed.

Five female mice were injected intravenously at 40 mL/kg with an extract of 2% sodium hyaluronate (120 hour/37^{o}C), with another five mice receiving the extract alone (0.9% NaCl). All animals were examined immediately, and 4, 48, 72, and 96 hours post-injection, and no signs of systemic toxicity were observed in either of the two treatment groups at any time point. The result showed that no significant reactions were shown. The result was acceptable.

Intracutaneous Reactivity Test

A toxicological study, Intracutaneous Reactivity, was conducted on the test sample sodium hyaluronate sterile syringe 16.0 mg/2 mL in order to provide data necessary to the evaluation of biocompatibility.

In the intracutaneous reactivity test, 0.2 mL of Gel-Syn was injected intradermally into five sites, one cm apart, on the right side of the back of each of three male New Zealand white rabbits, with the same volume of physiological solution being injected into corresponding sites on the contralateral side of the animals. At 24, 48 and 72 hours after treatment, each of injection sites was examined for erythema, eschar, and edema, scored as none, slight, moderate, or severe.

Erythema, eschar, or edema were not seen in the three animals at any of the injection sites/time points, irrespective of treatment (mean irritation index = 0.00). The result

showed that no evidence of a reaction was seen at any of the injected sites in the three animals, irrespective of the treatment administered. The result was acceptable.

Sensitization

Guinea Pig Maximization Test

A Guinea Pig Maximization Test was conducted on the test sample, sodium hyaluronate sterile syringe 16.0 mg/2 mL, in order to provide data necessary for the evaluation of biocompatibility. One-tenth milliliter of undiluted Gel-Syn (10 animals) or water for injection (5 animals) was injected intradermally into three sites on the backs of female Hartley albino guinea pigs, with site 1 receiving the test article or vehicle alone, site 2 the test article or vehicle mixed 1:1 with Freund's complete adjuvant (FCA), and site 3 FCA 1:1 emulsion in water. Six days later, the induction site was treated with 1.0 mL of 10% sodium lauryl sulfate to induce local irritation, thereby enhancing skin permeability, followed the next day with a topical booster consisting of the application of 1 mL of either undiluted Gel-Syn or vehicle under an occlusive patch. After 48 hours, the occlusive patch was removed, and 12 days later (Day 21) 0.5 mL of Gel-Syn or vehicle was applied for 24 hours under occlusion to the right or left clipped flank, respectively, of each of the animals in both treatment groups. One and two days following removal of the challenge patches, the application sites were scored for erythema/eschar and edema on a 5-point scale, with 0 = no erythema or edema and 4 = severe. At each of the observation periods following the challenge phase of the study, erythema/eschar and edema scores of 0 were recorded for all animals/sites examined, irrespective of treatment. No signs of erythema or edema were observed in any of the animals in either the test or control groups. The result showed that the test product, sodium hyaluronate sterile syringe 16.0 mg/2 mL (Sinovial), is considered to be nonsensitizing. The result was acceptable.

Implantation

Subcutaneous Implantation testing was conducted on the test sample, sodium hyaluronate sterile syringe 16 mg/2 mL, in order to provide data necessary for the evaluation of biocompatibility. One milliliter of Gel-Syn was implanted subcutaneously into four sites on the back of each of three, male New Zealand white rabbits (paravertebral zone, right side), while on the contralateral (left) side, physiological solution was injected as a negative control. Animals were sacrificed 4 weeks after treatment, with all implantation sites in the test and control animals being macroscopically examined for any evidence of a tissue reaction. Additionally, one site from each of the animals was also sampled for histopathologic processing and examination. The result showed that no evidence of a response to either preparation was observed following macroscopic or microscopic examination. The result was acceptable.

Shelf Life

Expiration dating for this device has been established and approved at 36 months at 20˚C to 25˚C. The protocol the sponsor used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study outside the United States to establish reasonable assurance of the safety and effectiveness of intra-articular injections of Gel-Syn in osteoarthritis, with data from this study providing the basis for the PMA approval decision. This study was conducted in general compliance with Good Clinical Practices and European local informed consent regulations The protocol was not submitted to CDRH in a formal IDE prior to implementation as the study to gain market approval for Gel-Syn in the treatment of OA was conducted in various countries throughout Europe. A summary of the clinical study is presented below.

A. Study Design

A prospective, randomized, double-blind, active control (commercial hyaluronan), non-inferiority study was conducted from November 2007 to July 2009 at 23 centers in six countries of Western Europe (Czech Republic, France, Italy, Switzerland, Slovakia, and Germany), enrolling 380 patients with mild-moderate knee osteoarthritis who were given weekly intra-articular injections of either Gel-Syn or commercial hyaluronan for three consecutive weeks. The primary efficacy parameter for this study was change from baseline in the 100 mm WOMAC pain subscore through 26 weeks after three injections of each of the test products, with a non-inferiority margin of 8 mm being employed for the comparison between the Gel-Syn and a commercially available hyaluronan.

Objectives

The purpose of the study was to evaluate the clinical efficacy and general tolerability of two different injectable hyaluronic acid preparations (Gel-Syn, IBSA vs commercial hyaluronan) when administered to patients with symptomatic knee osteoarthritis.

Methodology

Patient assessments included screening, X-rays, knee OA diagnosis, target knee determination, randomization, intra-articular injections, clinical examinations, WOMAC index, Lequesne index, and other secondary measures. Patients were to be treated once weekly for three consecutive weeks beginning at baseline, with follow-up visits at 4, 12 and 26 weeks post-treatment.

The control group received commercial hyaluronan, “a legally marketed alternative with similar indications for use.”

Treatment Duration

3 weeks

Treatment Product

Gel-Syn, 2 mL of 0.84 % sodium hyaluronate (IBSA, Pambio-Noranco, Switzerland)

Reference Therapy

Commercial hyaluronan, 2 mL

Dose

2 mL injected once a week for three consecutive weeks.

Administration Mode
Intra-articular injection

1. Clinical Inclusion and Exclusion Criteria

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

1. Patients of either sex;
2. Age, 40 – 80 years;
3. Kellgren & Lawrence radiological grade 2-3;
4. Primary knee osteoarthritis of the medial or lateral femoro-tibial compartment;
5. Mean WOMAC pain subscore at the target knee ≥40 mm and <80 mm on a 100 mm VAS following analgesic/NSAID washout;
6. At least three months duration;
7. Diagnosed according to American College of Rheumatology criteria; and
8. Who failed to respond sufficiently to analgesics and/or NSAIDs taken regularly, or responders intolerant of the regular use of analgesics and/or NSAIDs.

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

1. Age <40 and >80 years;
2. BMI ≥32 kg/m^2;
3. Secondary (post-traumatic) OA of the target knee;
4. Diagnosis of predominantly femoral-patello knee pain mainly related to femoral-patellar syndrome at the target knee;
5. No remaining joint space width at the target knee;
6. Symptomatic hip OA or any other condition that would interfere with the study assessments;
7. Severe varus or valgus deformity in the target knee, defined as >15° axis deviation on radiography;
8. History or current evidence of: inflammatory, infective or metabolic joint disease, recurrent clinical chondrocalcinosis, crystal arthropathies, osteo-articular pathologies differing from arthrosis, articular fracture, ochronosis, acromegaly, hematochromatosis, Wilson's disease, primary osteochondromatosis, heritable disorders or mutations in the gene encoding collagen;
9. Concomitant rheumatic disease;
10. Significant injury to the target knee in the past 6 months;
11. Previous joint replacement or arthroplasty on the target knee;
12. Arthroscopy, osteotomy or surgery on the target knee in the past year;
13. Any surgical procedure scheduled in the next 6 months;
14. Venous or lymphatic stasis in the relevant limb;
15. Skin infection, disease or trauma at the injection site;
16. Systemic or intra-articular (target knee) corticosteroids in the past 3 months;
17. Intra-articular corticosteroids (contralateral knee) in the past 4 weeks;
18. Viscosupplementation to the target knee in the past year;
19. Initiation of target knee physical therapy in the past 3 months;

20. Initiation or change in dose of SYSADOA therapy;
21. Ongoing anticoagulant therapy;
22. Chronic or recurrent use of NSAIDs, analgesics or narcotics resulting from disease(s) other than osteoarthritis of the target knee;
23. History of allergy or hypersensitivity to hyaluronic acid, paracetamol or avian proteins;
24. Participation in a clinical study within the past 3 months;
25. Pregnant or lactating women, and women of childbearing potential not willing to use adequate contraception; and
26. Individuals unwilling to remain in the study for 6 months, or those unable to understand or cooperate with study requirements.

2. Follow-up

Screening and Selection Procedures

Prospective patients were presented with a description of the trial, and those willing to participate provided written informed consent (**Visit 0**). At this time, the patient received a four digit screening number (Center Number = Digit 1 and 2; Patient Number = Digit 3 and 4, assigned in consecutive order beginning with 01), which, along with their initials (first letter of first name and first letter of last name), permitted identification during the trial. After obtaining consent, the Investigator recorded demographic data, medical history, and concomitant medication usage, as well as the location and number of symptomatic osteoarthritic joints. A general physical and knee examination were also performed, the latter including assessment of range of motion, effusion, and distal leg angulation (varus or valgus). For women of childbearing potential, a urine sample was collected for pregnancy testing. Knee OA was characterized by determining the side of involvement, date of first diagnosis, duration since symptoms began, duration since pain began, history of significant trauma, most painful knee within 3 months, global pain score on a 0-100 mm VAS, pain score within the past week (1-10 scale), global status scored by the patient (0-10 scale), pain frequency within the past month (continuous or intermittent, with number of flare-ups), number of days of pain within the past month, number of nights sleep interrupted by pain within the past month, presence of crepitus, presence and duration of morning stiffness, ambulatory assistance (insoles, canes, crutches, braces), surgical procedures including the date of the most recent procedure, date and description of pharmacologica1 and non-pharmacological intervention within the past year (systemic or intra-articular corticosteroids, SYSADOA, intra-articular hyaluronic acid, articular lavage), frequency of NSAID and analgesic consumption within the past month and date of last dose, responsiveness to repeated NSAID and analgesic therapy, adverse events related to the repeated use of NSAIDs and analgesics, other therapy within the past year (physiotherapy, mesotherapy, acupuncture, weight reduction program), prior history of, or recurrent hydrarthrosis, number of knee joint effusion episodes within the past year, number of knee aspirations and intra-articular steroid injections within the past year, number of doctor visits for knee OA within the past year, and number of lost work days/days of total inactivity within the past year.

Patients were asked about imaging of the affected knee(s). If X-ray images were available, and collected within the past 6 months, they were used for diagnostic confirmation and grading of OA, and stored in the patient's file. If unavailable, both knees were imaged within 10 days on the same film in the extended knee antero-posterior weight bearing view. During this trial, only one knee per patient was used for treatment and evaluation. In the event of bilateral OA, the most seriously affected knee was selected, based upon both patient and Investigator perception.

Patients were also asked about consumption of NSAIDS and analgesics. If these medications had been consumed within 5 days of the screening visit, a wash-out phase lasting 5-10 days was instituted. Since NSAID and analgesic use were prohibited during the trial, patients were provided with rescue medication (500 mg paracetamol tablets), and asked to record consumption (tablets per day) in a diary, which was also used by patients to describe changes in concomitant medication, lifestyle or adverse events. The investigator counseled patients against the use of any palliative agents during the study and reminded them to bring the diary and rescue medication to each visit.

Patients with available X-rays, and not requiring a wash-out phase, were immediately subjected to a baseline evaluation **(Visit 1).** In these cases, Visit 0 and 1 occurred on the same day.

Baseline and Inclusion

Five to ten days after the screening visit, patients who required medication wash-out or X-rays were subjected to a baseline evaluation **(Visit 1).** First, however, the Investigator recorded adverse events and consumption of both concomitant and rescue medication as captured by the diary. In addition, the target joint and/or future injection site were examined to determine range of motion, skin integrity and the presence of effusion, as it was for the patients whose screening and baseline visit were coincident.

The screening phase for all patients was completed following evaluation of the WOMAC questionnaire, and study eligibility was determined by assessing compliance with the inclusion/exclusion criteria. Eligible patients were assigned a three-digit randomization number in chronological order (beginning with 001), which was subsequently used for identification purposes. Baseline pain and disability were then established using the Lequesne questionnaire, global pain assessment on the target and contralateral knee, and global patient status as defined by the patient and Investigator.

Patients received a one-month supply of rescue medication and were instructed not to consume the medication in the 24 hours preceding a study visit, with rescue medication consumption being recorded in a diary, along with concomitant medication usage, adverse events, lifestyle changes and the weekly global pain assessment. The Investigator reminded the patients to return for the next visit with the diary and rescue medication box. The patient then received the first intra-articular

injection of Gel-Syn or commercial hyaluronan into the target knee. The patient's randomization number dictated which product was administered, and the identity of that product was concealed from both the patient and Investigator. Subsequently, the patient assessed pain at the injection site.

Treatment Phase
Patients returned to the study site each of the next two weeks (**Visits 2** and **3**; 7 ± 1 and 14 ± 1 days from Visit 1, respectively). During these visits, the Investigator recorded adverse events, consumption of concomitant and rescue medication and patient-assessed local tolerability at the injection site, reviewed the diary, examined the target joint for effusion and the injection site for skin integrity. Intra-articular injection of the assigned product was then performed, and the patient evaluated pain at the injection site. The Investigator reminded the patients to return for the next visit with the diary and rescue medication boxes.

Follow-Up
Patients returned to the study site at 4, 12 and 26 weeks from the date of initial injection (Visits 4 -6; 28 ± 2, 84 ± 3 and 182 ± 7 days from Visit 1, respectively). During these visits, the Investigator measured the patient's body weight, recorded adverse events, consumption of concomitant and rescue medication and patient-assessed local tolerability at the injection site, reviewed the diary, and examined the target joint for effusion and range of motion. In addition, the investigator completed the Lequesne questionnaire and assessed the patient's global status. The patient completed the WOMAC questionnaire and assessed global pain, status and tolerability. As needed (Visits 4, 5), patients were provided with additional rescue medication. The Investigator reminded the patients to return for the next visit with the diary and rescue medication boxes.

Visits not defined by the protocol were permitted if the Investigator considered them necessary for the patient's well-being. Any data collected during these visits were only used for the safety analysis. If one of these visits led to study discontinuation, all assessments specified in the protocol for the next scheduled visit were to be performed.

Final Visit
Twenty-six weeks after the first intra-articular injection, patients returned to the site for the final visit (**Visit 6**), which consisted of the activities described under Follow-up above, as well as collection of rescue medication and diaries.

Adverse events and complications were recorded at all visits.
The key time-points are shown below in the tables summarizing safety and effectiveness over 4 to 26 weeks.

3. Clinical Endpoints
With regards to safety, the following were assessed.
• Adverse events;

• Pain at injection site;
• Local tolerability at injection site:
• Global tolerability (patient and investigator)

Primary Efficacy Variable
Western Ontario McMaster Universities (WOMAC) pain subscore.

Secondary Efficacy Variables
• WOMAC total score and pain, stiffness and function subscores;
• Lequesne Algofunctional Index;
• Global pain assessed by patient;
• Global status assessed by patient;
• Global status assessed by Investigator;
• Paracetamol consumption;
• Patient satisfaction;
• Overall response based on OMERACT-OARSI criteria.

B. Accountability of PMA Cohort

At the time of database lock, 380 patients were enrolled in PMA study, with demographic data being provided in **Table 1** below.

Table 1: ITT Patients – Demographics

Continuous Variable	N	Mean ± SD	Range
Age (years)	380	65.0 ± 8.9	41.8 to 80.9
Height (cm)	380	166.6 ± 8.0	148 to 193.0
Weight(kg)	380	75.2 ± 11.5	50.0 to 110.0
BMI(kg/m^2)	380	27.0 ± 3.1	19.8 to 34.7

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are comparable to those of the United States, as shown in the above table.
The average age of the 380 intent-to-treat (ITT) patients, defined as receiving at least one intra-articular injection, was 65.0 years, the majority were female (72.9%), BMI ranged from 19.8 to 34.7 kg/m^2, and the mean duration of osteoarthritis in the target knee was 7.61 years. For 52.6% of the patients, the right knee was the target knee, but 66.1% also had osteoarthritis in the contralateral knee. The anatomical location of target knee osteoarthritis was usually in the medial tibio-femoral region (82.9%), with some degree of joint space narrowing being reported in nearly all patients (95.0%). Patient assessed global pain scores at the screening and baseline visits averaged 65.3 and 65.6, respectively, while the other indices of disease severity at these time-points (i.e. global status, range of motion, WOMAC & Lequesne scoring) were also suggestive of mild to moderate target knee osteoarthritis. The only baseline variable reaching statistical significance with regard to differences between the two treatment groups was venous insufficiency which

was more prevalent for commercial hyaluronan patients (5.3% vs 1.0%, p =0.019), with hypercholesterolemia and the requirement for ambulatory assistance also being somewhat (but not statistically significantly) greater (11.7% vs 6.3%, p = 0.073 and 5.9% vs 2.1%, p = 0.069, respectively).

D. Safety and Effectiveness Results

1. Safety Results

Adverse Events – Of the 380 patients (192 subjects for Gel-Syn, and 188 for Commercial Hyaluronan) in the intent-to-treat (ITT) patient population, one or more adverse events were recorded for 160 patients (42.1%) sometime over the course of the study following the first injection of the assigned hyaluronic acid preparation, by far the most common being back pain (11.8%), arthralgia (10.5%), nasopharyngitis (8.9%), and headache (8.2%). Back pain, arthralgia, and headache were more common in the commercial hyaluronan treatment group than in the Gel-Syn treatment group (**Table 2**). Adverse events judged to be related to treatment, severe and/or serious were relatively rare (1.6%), and none of the serious adverse events were thought to be treatment-related (**Table 3**). Overall adverse event rates for the Gel-Syn treatment group were comparable to those of the commercial hyaluronan treatment group.

Pain at Injection Site/Local Tolerability – Pain associated with the initial injection of the experimental product or comparator in ITT patients averaged 2.95 on a 10 point scale, declining slightly to 2.80 then 2.65 after the second and third injections, respectively, with local tolerability being judged as good/very good by 91% to 93% of the patients at each of the visits following product administration.

Patient/Investigator Global Tolerability – Patient and investigator assessed global tolerability at the 4, 12 and 26 week follow-up visits were nearly identical and comparable to local tolerability scoring, as good/very good scores were obtained from 93% to 97% of the respondents. There were no statistically significant intergroup differences for any of these variables.

Table 2: ITT Patients – Adverse Events*

* Adverse events are included in this table only if the incidence in one of the treatment groups exceeded 1%.
† First n is number of events, and second n is number of patients experiencing an event.

‡ Fisher's exact test.		Gel-Syn (N=192)			Commercial Hyaluronan (N=188)		
Variable	n†	n	Percent	n	n	Percent	p Values‡
Any Adverse Event	222	83	43.2%	220	77	41.0%	0.679
Gastrointestinal Disorders							
Toothache	8	7	3.6%	3	3	1.6%	0.337
Diarrhea	1	1	0.5%	4	3	1.6%	0.368
Abdominal pain upper	0	0	0.0%	2	2	1.1%	0.244
General Disorders/Administrative Site Conditions							
Pyrexia	6	5	2.6%	7	5	2.7%	1.000
Injection site pain	3	1	0.5%	4	3	1.6%	0.368
Hepatobiliary disorders							
Cholecystitis acute	0	0	0.0%	2	2	1.1%	0.244
Infections and infestations							
Nasopharyngitis	27	19	9.9%	22	15	8.0%	0.591
Respiratory tract infection	4	4	2.1%	3	3	1.6%	1.000
Urinary tract infection	4	4	2.1%	3	3	1.6%	1.000
Influenza	6	3	1.6%	3	3	1.6%	1.000
Cystitis	1	1	0.5%	5	4	2.1%	0.211
Herpes zoster	0	0	0.0%	2	2	1.1%	0.244
Viral infection	1	1	0.5%	2	2	1.1%	0.620
Musculoskeletal/Connective Tissue Disorders							
Back pain	25	19	9.9%	39	26	13.8%	0.268
Arthralgia	29	18	9.4%	28	22	11.7%	0.506
Pain in extremity	9	9	4.7%	4	2	1.1%	0.062
Musculoskeletal pain	6	5	2.6%	2	2	1.1%	0.449
Neck pain	3	1	0.5%	5	4	2.1%	0.211
Joint swelling	2	2	1.0%	5	2	1.1%	1.000
Nervous System Disorders							
Headache	29	13	6.8%	31	18	9.6%	0.353
Respiratory/Thoracic/Mediastinal Disorders							
Oropharyngeal pain	3	3	1.6%	2	2	1.1%	1.000

Table 3: ITT Patients – Adverse Events Based on Relationship to Treatment, Severity, Seriousness

* First n is number of events, and second n is number of patients experiencing an event.
† Fisher's exact test.

	Gel-Syn (N=192)			Commercial Hyaluronan (N=188)			
Variable	n*	n	Percent	n	n	Percent	p Values†
Adverse Events Certainly, Probably Related to Treatment							
Any Adverse Event	1	1	0.5%	5	4	2.1%	0.211
General disorders and administration site conditions							
Injection site hematoma	0	0	0.0%	1	1	0.5%	0.495
Injection site pain	1	1	0.5%	1	1	0.5%	1.000
Musculoskeletal and connective tissue disorders							
Arthralgia	0	0	0.0%	1	1	0.5%	0.495
Joint swelling	0	0	0.0%	2	1	0.5%	0.495
Severe Adverse Events							
Any Adverse Event	1	1	0.5%	6	6	3.2%	0.065
Gastrointestinal Disorders							
Diverticulum intestinal	0	0	0.0%	1	1	0.5%	0.495
Hepatobiliary disorders							
Cholecystitis acute	0	0	0.0%	1	1	0.5%	0.495
Infections and infestations							
Influenza	0	0	0.0%	1	1	0.5%	0.495
Injury, poisoning and procedural complications							
Radius fracture	0	0	0.0%	1	1	0.5%	0.495
Musculoskeletal and connective tissue disorders							
Arthritis	0	0	0.0%	1	1	0.5%	0.495
Intervertebral disc protrusion	1	1	0.5%	0	0	0.0%	1.000
Surgical and medical procedures							
Hip arthroplasty	0	0	0.0%	1	1	0.5%	0.495
Serious Adverse Events							
Any Adverse Event	2	2	1.0%	5	4	2.1%	0.445
Gastrointestinal disorders							
Abdominal wall hematoma	1	1	0.5%	0	0	0.0%	1.000
Diverticulum intestinal	0	0	0.0%	1	1	0.5%	0.495
General disorders and administration site conditions							
Pyrexia	0	0	0.0%	1	1	0.5%	0.495
Hepatobiliary disorders							
Cholecystitis acute	0	0	0.0%	1	1	0.5%	0.495
Musculoskeletal and connective tissue disorders							
Arthritis	0	0	0.0%	1	1	0.5%	0.495
Intervertebral disc protrusion	1	1	0.5%	0	0	0.0%	1.000
Surgical and medical procedures							
Hip arthroplasty	0	0	0.0%	1	1	0.5%	0.495

2. Effectiveness Results

Primary Endpoint – The protocol violations for the two groups were comparable, and the lower confidence interval for the difference between Gel-Syn-treated patients (n=192) and those given commercial hyaluronan (n=188) with regard to the primary efficacy endpoint (100 mm WOMAC pain subscore) was -1.4 when analyzed using a repeated measures mixed model of analysis of covariance, a value above the study non-inferiority margin of -8.0 (**Table 4**), Overall WOMAC pain subscore mean reduction from baseline was 30.8 mm (56%) for the Gel-Syn treatment group, in contrast to 29.4 mm (53%) for patients receiving commercial hyaluronan.

Table 4: Primary Endpoint (100 mm WOMAC Pain Subscore)* for Intent-To-Treat

	Gel-Syn		Commercial Hyaluronan			
Variable	N	Mean ± SE	N	Mean ± SE	Difference*	95% CI
Absolute Values						
Baseline	192	55.2 ± 0.8	188	55.5 ± 0.8	-0.3 ± 1.1	(-2.5, 1.9)
4 Weeks	189	27.0 ± 1.6	183	28.6 ± 1.7	-1.6 ± 1.7	(-4.9, 1.7)
12 Weeks	185	23.6 ± 1.6	178	25.6 ± 1.7	-2.0 ± 1.7	(-5.4, 1.4)
26 Weeks	181	22.2 ± 1.6	175	22.9 ± 1.7	-0.7 ± 1.7	(-4.1, 2.7)
Overall	.	24.3 ± 1.5	.	25.7 ± 1.6	-1.4 ± 1.5	(-4.3, 1.4)
Change from Baseline						
4 Weeks	189	28.1 ± 1.6	183	26.5 ± 1.7	1.6 ± 1.7	(-1.7, 4.9)
12 Weeks	185	31.5 ± 1.6	178	29.5 ± 1.7	2.0 ± 1.7	(-1.4, 5.4)
26 Weeks	181	32.9 ± 1.6	175	32.2 ± 1.7	0.7 ± 1.7	(-2.7, 4.1)
Overall	.	30.8 ± 1.5	.	29.4 ± 1.6	1.4 ± 1.5	(-1.4, 4.3)
* Gel-Syn minus Commercial Hyaluronan ± SE.						
Mixed models include factors for treatment, visit, treatment*visit interaction, center and baseline level.						

Secondary Efficacy Variables:

- WOMAC total score and pain, stiffness and function subscores;
- Lequesne Algofunctional Index;
- Global pain assessed by patient;
- Global status assessed by patient;
- Global status assessed by Investigator;
- Paracetamol consumption;
- Patient satisfaction;
- Overall response based on OMERACT-OARSI criteria.

For the secondary study variables, because this was a non-inferiority study not designed to test superiority, no claims can be made about the statistical significance

of any intergroup differences such as those observed at 26 weeks following either three Gel-Syn or commercial hyaluronan injections (**Table 5**).

Table 5: Secondary Outcome Variables at 26 Weeks

	Gel-Syn (N=192)		**Commercial Hyaluronan (N=188)**		
Variable*	N	Mean ± SE or %	N	Mean ± SE or %	p
1. WOMAC Function	181	28.3 ± 1.7	175	28.0 ± 1.8	0.860
2. WOMAC Stiffness	181	25.9 ± 1.8	175	25.2 ± 1.9	0.735
3. WOMAC Total Score	181	29.0 ± 1.6	175	28.6 ± 1.7	0.811
4. Lequesne Pain	181	2.08 ± 0.16	175	1.79 ± 0.17	0.097
5. Lequesne Walking	181	0.79 ± 0.10	175	0.66 ± 0.11	0.262
6. Lequesne Daily Living	181	1.23 ± 0.12	175	1.10 ± 0.13	0.320
7. Lequesne Total Score	181	4.07 ± 0.32	175	3.53 ± 0.33	0.124
8. Patient Global Pain	181	37.2 ± 2.2	175	33.6 ± 2.3	0.138
9. Patient Global Status	180	25.4 ± 2.0	175	25.7 ± 2.1	0.892
10. Paracetamol Usage	187	46.8 ± 9.7	183	62.8 ± 10.1	0.090
11. Patient Satisfaction	181	82.9%	174	77.0%	0.185
12. Investigator Global Status	181	85.0%	174	76.5%	0.043
13. OMERACT-OARSI	181	89.9%	175	87.7%	0.504
1 to 9: 26-Week Change from Baseline Score (higher=better). Mixed models include factors for treatment, visit, treatment*visit interaction, center and baseline level.					
10: Number of paracetamol rescue medication tablets over the entire 26 Weeks. Mixed model includes factors for treatment and center.					
11: Patients satisfied or very satisfied at 26 Weeks. Generalized Estimating Equation (GEE) logistic regression model includes factors for treatment, visit, treatment*visit interaction and center.					
12: Status good or very good at 26 Weeks. Generalized Estimating Equation (GEE) logistic regression model includes factors for treatment, visit, treatment*visit interaction, center and baseline level.					
13: OMERACT-OARSI Success at 26 Weeks. Generalized Estimating Equation (GEE) logistic regression model includes factors for treatment, visit, treatment*visit interaction and center.					

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 25 foreign investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Advisory 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

The effectiveness of Gel-Syn (n=192) in reducing the Western Ontario McMaster Universities (WOMAC) pain subscore at 26 weeks in osteoarthritis patients was shown to be non-inferior to commercial hyaluronan (n=188) with a delta of 8 mm (p=0.001). The difference in change from baseline for these two preparations (Gel-Syn minus commercial hyaluronan) was 1.4, with the lower and upper 95% confidence interval of the difference being -1.4, 4.3.

The worst case difference (Gel-Syn minus Commercial Hyaluronan) with regard to the primary efficacy endpoint (100 mm WOMAC pain subscore) was -1.4, a value above the study non-inferiority margin of -8.0. Overall WOMAC pain subscore mean reduction from baseline was 30.8 mm (56%) for the Gel-Syn treatment group, in contrast to 29.4 mm (53%) for patients receiving commercial hyaluronan. The two groups were comparable to each other in effectiveness.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies as well as data collected in a clinical study conducted to support PMA approval as described below.

Of the 380 patients in the ITT patient population, one or more adverse events were recorded for 160 (42.1%) sometime over the course of the study following the first injection of the assigned hyaluronic acid preparation, by far the most common being back pain (11.8%), arthralgia (10.5%), nasopharyngitis (8.9%), and headache (8.2%). Back pain, arthralgia, and headache were more common in the commercial hyaluronan treatment group than in the Gel-Syn treatment group. Adverse events judged to be related to treatment, severe and/or serious were relatively rare (1.6%), and none of the serious adverse events were thought to be treatment-related. Overall adverse event rates for the Gel-Syn treatment group were comparable to those of the commercial hyaluronan treatment group, and the device is judged to be reasonably safe.

C. Benefit-Risk Conclusions

The probable benefit of the device, based on data collected in a clinical study conducted to support PMA approval as described above, is to decrease pain in knee osteoarthritis. The device was compared to three injections of commercial hyaluronan

in the amount of pain reduction over 26 weeks. The effectiveness of Gel-Syn with regard to other parameters, such as WOMAC total score and pain, stiffness and function subscores was also evaluated over the course of the above study, but no claims can be made about the statistical significance of any intergroup differences observed. The risk of using this device poses minimal risk to a patient, such as arthralgia and injection site pain.

In conclusion, the data from the clinical trial above support the claim that for reduction of pain in osteoarthritis of the knee, the probable benefits of Syn-Gel outweigh the probable risks.

D. Overall Conclusions

The data in this PMA application support the reasonable assurance of safety and effectiveness of this device when used in accordance with indications for use. Adverse events judged to be related to treatment, severe and/or serious were relatively rare (1.6%), and none of the serious adverse events were thought to be treatment-related (**Table 4**). Overall adverse event rates for the Gel-Syn treatment group were comparable to those of the commercial hyaluronan treatment group. For the primary outcome measure (change from baseline), the protocol-defined 8 mm non-inferiority margin was met for all time points. In addition, the 95% lower-bound confidence interval of the difference (Gel-Syn minus commercial hyaluronan) in pain subscore reduction from baseline for the overall 26 week WOMAC pain subscore for the ITT patient population was -1.4. Overall WOMAC pain subscore mean reduction from baseline was 30.8 mm (56%) for the Gel-Syn treatment group, in contrast to 29.4 mm (53%) for patients receiving commercial hyaluronan.

XIII. CDRH Decision

CDRH issued an approval order on May 9, 2014.

The applicant's manufacturing facilities were 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.