SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

DEVICE GENERIC NAME: Hylan G-F 20

DEVICE TRADE NAME: Synvisc®

APPLICANT'S NAME: Biomatrix, Incorporated
65 Railroad Avenue
Ridgefield, NJ 07657

PREMARKET APPROVAL (PMA) APPLICATION NUMBER: P940015

DATE OF PANEL RECOMMENDATION: November 20, 1996

DATE OF NOTICE OF APPROVAL TO THE APPLICANT: August 8, 1997

II. INDICATIONS FOR USE

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

III. DEVICE DESCRIPTION

Synvisc® (hylan G-F 20) is an elastoviscous fluid containing hylan polymers produced from chicken combs. Hylans are derivatives of hyaluronan (sodium hyaluronate), a natural complex sugar of the glycosaminoglycan family. Hyaluronan is a long-chain polymer containing repeating disaccharide units of Na-glucuronate-N-acetylglucosamine.

Synvisc® contains hylan A (average molecular weight 6,000,000) and hylan B hydrated gel in a buffered physiological sodium chloride solution, pH 7.2. Synvisc® has an elasticity (storage modulus G') at 2.5 Hz of 111 ± 13 Pascals (Pa) and a viscosity (loss modulus G") of 25 ± 2 Pa (elasticity and viscosity of knee synovial fluid of 18-27 year old humans measured with a comparable method at 2.5 Hz: G' = 117 ± 13 Pa; G" = 45 ± 8.2 Pa).

Synvisc® is supplied in a 2.25 mL glass syringe containing 2.0 mL Synvisc®. The contents of the syringe are sterile and nonpyrogenic.

Each syringe of Synvisc® contains:

Hylan polymers (hylan A + hylan B)	16 mg
Sodium chloride	17 mg
Disodium hydrogen phosphate	0.32 mg
Sodium dihydrogen phosphate monohydrate	0.08 mg
Water for injection	q.s. to 2.0 mL

Information concerning the following sections of this Summary of Safety and Effectiveness Data is included in the product labeling at the end of this document:

IV. CONTRAINDICATIONS

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

Precautions and warnings can be found in the device labeling.

V. ALTERNATIVE PRACTICES AND PROCEDURES

For patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, e.g., acetaminophen, alternative therapies to Synvisc® include nonsteroidal anti-inflammatory drugs (NSAIDs); intraarticular injections of corticosteroids or injections of unmodified hyaluronan (sodium hyaluronate). For patients who have failed the above treatments, surgical interventions such as arthroscopic surgery and total knee replacement surgery are also alternative treatments.

VI. POTENTIAL ADVERSE EFFECTS

A total of 511 subjects (559 knees) received 1771 injections in seven clinical trials of Synvisc®. There were 37 reports in 35 subjects (2.3% of injections, 7% of subjects) of knee pain and/or swelling after these injections.

Ten subjects (10 knees) were treated with arthrocentesis and removal of joint effusion. Two additional subjects (two knees) received treatment with intra-articular steroids. Two subjects (two knees) received NSAIDs. One of these subjects also received arthrocentesis. One subject was treated with arthroscopy. The remaining subjects with adverse events localized to the knee received no treatment or only analgesics.

Systemic adverse events occurred in 10 (2.0%) of the Synvisc® treated subjects. There was one case each of rash (thorax and back) and itching of the skin following Synvisc® injections in these studies. These symptoms did not recur when these subjects received additional Synvisc® injections. The remaining generalized adverse events reported were calf cramps, hemorrhoid problems, ankle edema, muscle pain, tonsillitis with nausea, tachyarrythmia, phlebitis with varicosities and low back sprain.

In three concurrently controlled clinical trials with a total of 112 subjects who received Synvisc® and 110 subjects who received either saline or arthrocentesis, there were no statistically significant differences in the

numbers or types of adverse events between the group of subjects that received Synvisc® and the group that received control treatments.

In clinical use in Canada (since 1992) and Sweden (since 1995), the most common adverse events reported have been pain, swelling, and/or effusion in the injected knees. Other adverse events reported were one case each of: generalized urticaria; recurring small hives; pain on one side of the body with nausea, anxiety and listlessness; facial flush with swelling of lips; nausea with dizziness; shivering with headache, nausea, respiratory difficulties; and prickling in body which did not recur after subsequent Synvisc® injections. No cases of anaphylaxis or anaphylactoid reactions have been reported. No deaths have been associated with the use of Synvisc®. Intra-articular infections did not occur in any of the clinical trials, but have occurred in clinical use following Synvisc® injections.

VII. MARKETING HISTORY

Synvisc® has been manufactured and marketed in Canada since November, 1992, and in Sweden since June, 1995. CE Mark Approval was granted in the European Community in November, 1995. Synvisc® has not been withdrawn from marketing in any countries.

VIII. SUMMARY OF PRECLINICAL STUDIES

Synvisc® (hylan G-F 20) and each of its two components (hylan A and hylan B) were studied in nonclinical laboratory studies to characterize their biological properties and to ensure safety.

Irritation tests: Hylan A, hylan B and Synvisc® (hylan G-F 20) were each evaluated in intracutaneous toxicity studies in NZW rabbits using the USP method. A volume of 0.2 ml was injected into each of five intradermal sites. Injection sites were examined 24, 48, and 72 hours post-injection for erythema and edema. No evidence of significant irritation or of other signs of local toxicity was observed in any of the studies. It was concluded that neither Synvisc® nor its two components induced irritation.

Sensitization and immunogenicity assays: Dermal sensitization potential was evaluated for hylan A, hylan B and Synvisc® using the test described by Magnusson and Kligman, 1970. Following two induction phases, each of 10 treated guinea pigs were challenged with undiluted test material (hylan A, hylan B or Synvisc®) using a Hill Top chamber. At 24, 48, 72 and 96 hours, the dermal reaction was evaluated according to Draize criteria. Synvisc®, hylan A and hylan B did not induce detectable dermal sensitization under the test conditions.

The immunogenicity of Synvisc® was also evaluated in primates. Twenty owl monkeys received weekly bilateral intra-articular injections of Synvisc® for six months. Monthly dermal challenge testing for up to 31 weeks produced negative skin test results indicative of an absence of cell-mediated immunity. Serum analysis by ELISA, carried out monthly through six months and at one year, gave no indication of humoral immunity.

Cytotoxicity: Hylan A, hylan B and Synvisc® were assessed for cytotoxicity using in vitro methods (MEM elution method, current USP procedure) in L929 mouse fibroblast cell line. None of the hylans produced cell lysis or cytotoxicity under the conditions tested.

Acute systemic toxicity: Hylan A, hylan B and Synvisc® were evaluated for systemic toxicity in mice using the USP procedure. A dose of 50 ml per kg of test article was administered intraperitoneally to each animal. Mice were observed for adverse reactions at four, 24, 48 and 72 hours. None of the test articles appeared to be systemically toxic in mice.

Eight studies of acute toxicity were conducted in NZW rabbits following intra-arterial, intra-articular, subcutaneous and subconjunctival administration of hylan preparations. Mild to moderate focal or multifocal inflammations of the synovial membranes were observed seven days after intra-articular injections of the hylans in one study. These were not found in joints studied four weeks after such injections.

Hemocompatibility: The hemocompatibility of hylan A, hylan B and Synvisc® was evaluated in three in vitro hemolysis studies in which the USP direct contact method was used. Hylan A, hylan B and Synvisc® did not show any hemolytic activity in these studies.

Eleven studies were carried out to evaluate the effect of hylan A, hylan B and Synvisc® on platelet function and blood clotting. None of the studies produced evidence that Synvisc® and its components (hylan A and hylan B) interfere with platelet function or with the clotting mechanism.

Pyrogenicity: In the rabbit pyrogen test (USP test for material-mediated pyrogenicity), Synvisc® (reduced elastoviscosity) was injected intravenously into NZW rabbits in a single dose of 10 ml/kg of diluted test article. The body temperature of the rabbits was then measured during a three-hour observation period. No elevations in body temperature were observed in rabbits injected with the Synvisc® preparation or with samples taken from 14 batches of hylan A and from five batches of hylan B.

Tissue Implantation: Seven-day and 30-day intramuscular implantation studies were conducted in rabbits using hylan A, hylan B or Synvisc®. All hylan test articles produced macroscopic responses that were comparable to a negative control implant material.

Ten studies using rats, guinea pigs and owl monkeys were conducted to characterize any tissue reactions to implanted hylans. Hylan B was injected subcutaneously (5 ml) into each of 28 female rats. Saline was injected into eight rats, which served as controls.

A small amount of fibrosis was noted in 75% of the injection sites three months after hylan B implantation. Hylan B remained present in the injection site 12 months after implantation, but was not associated with fibrosis or with any other tissue reaction.

Sixteen guinea pigs were injected at multiple sites with either hylan B, injectable collagen (Zyplast® and Zyderm®, Collagen Corp.) or physiological saline. Tissue samples were taken from two animals at each of the following time points: three days and one, two, four, nine, 13, 26 and 52 weeks. Hylan B proved to be biocompatible and remained present 52 weeks after injection. The collagen implants could not be detected at Week 52.

The liquid vitreous of owl monkeys was replaced with hylan A, hylan B, and Synvisc® in the monkey vitreous test (Balazs and Denlinger, 1980). The inflammatory reaction was quantified by measuring the level of infiltration of leukocytes into the anterior chamber 48 hours after insertion of the hylan test article. Ocular changes were evaluated using slit lamps, ophthalmoscopy, and measurements of intraocular pressure periods for up to 74 months. Hylan A, hylan B and Synvisc® produced no inflammation or any other evidence of toxicity in any of the tested eyes.

Mutagenicity: Hylan A, hylan B and Synvisc® were evaluated for mutagenic and clastogenic potential in a series of test procedures, which included the Ames assay, a chromosome aberration assay in Chinese hamster ovary (CHO) cells (Hsie et al.), a CHO/hypoxanthine guanine phosphoribosyl transferase (HGPRT) mutation assay, and an unscheduled DNA synthesis (UDS) assay. The hylan materials were not found to be mutagenic or clastogenic in any of these tests.

Synvisc®, hylan A, and hylan B (degraded and intact) were evaluated in the plate incorporation assay (gene mutation assay, Ames et al.). All assays included activated (S-9 fraction of rat liver homogenate from Aroclor 1254-induced rats) and non-activated systems. None of the hylan preparations produced evidence of mutagenicity.

The ability of Synvisc® to induce chromosome aberrations was tested using cultured CHO cells with and without metabolic activity. Synvisc® did not induce any chromosomal abnormalities in any these tests.

Synvisc® was tested for its ability to induce gene mutation at the HGPRT locus in cultured CHO cells, with and without an exogenous S-9 activation system at a range of various concentrations. Synvisc® showed no indication of mutagenic activity at any dose tested.

Synvisc® was tested for its potential to cause unscheduled DNA synthesis (UDS) in rat primary hepatocytes (Mirsalis and Butterworth). Hepatocytes were obtained from Sprague-Dawley rats that had been treated intraperitoneally with three doses of Synvisc®. UDS was evaluated by measuring the incorporation of [^{3}H]-thymidine into the extracted hepatocytes. None of the three doses of Synvisc® appeared to produce any increase in UDS or any primary DNA damage.

Subchronic toxicity: Five parenteral repeat-dose toxicity studies of two-week to five-week duration were conducted in guinea pigs and rabbits to determine potential toxicity of hylan A and hylan B, the two components of Synvisc®. Hylan A and hylan B did not produce any remarkable systemic or local toxicity. Individual summaries of the studies are given below:

Hylan A, when administered in two weekly intraperitoneal injections of 10 mg/ml (2.5 ml/kg to each group of male and female test animals), produced no changes in body weight or organ weights. Hematology and clinical chemistry comparisons were similar to that of control animals. No treatment-related gross or microscopic changes were observed.

Four weekly intra-arterial injections of hylan A (3 mg/kg) produced no changes in body weights, clinical pathology parameters or blood hyaluronan levels in 14 NZW rabbits. No gross or histological treatment-related changes were observed.

Knee joints of 10 male rabbits were injected bilaterally with 0.5 ml of hylan B (2.6 mg/ml), or physiological saline solution twice at an interval of one week. Animals were sacrificed 3 weeks after the second injection. Body weight and clinical pathology values were not affected by the treatment. Minimal focal or multifocal inflammation in synovial membranes was associated with the treatment.

Four consecutive weekly intra-articular injections of hylan A (0.3 ml/joint) into the knee joints (bilateral) of five NZW rabbits produced no changes in normal weight gains. At the end of the fourth week, no changes were found in synovial fluid volume and its hyaluronan content and hexuronic acid or hexosamine content of joint cartilage. No immunogenic skin responses (erythema and edema) or gross joint abnormalities were observed in any animals in this study.

Chronic toxicity in primates: Synvisc® was tested in owl monkey joints for its potential to induce local and systemic effects following repeated weekly bilateral intra-articular (knee) injections for 31 weeks (average of 24 injections per knee) with a one-year follow-up period. The study consisted of two groups of animals: a treatment group of 20 (eight male and 12 female) monkeys and a control group of 14 (six male and eight female) monkeys. The animals in the treatment group received an amount of Synvisc® that <u>in toto</u> represented a dose that was greater than 20 times the total human clinical regimen when adjusted for body mass.

The following parameters were evaluated in this study: clinical signs (specifically related to the functions and health of the joint) and behavioral changes (daily); body weight gains (monthly); intradermal skin sensitization testing (monthly); blood sampling for immune reactivity by ELISA methodology (monthly); and determination of hematology and clinical chemistry parameters and urinalysis (at 16 or 21 months after the first injection).

Synvisc® was not associated with any detectable local or systemic adverse effects during the observation period. No detectable changes related to overall health, behavior or physical activity were observed that appeared related to Synvisc® treatment. There were no clinical signs of any local reactions (swelling, heat, redness) to Synvisc® in the knees or the legs.

Analysis of hematology, clinical chemistry and urinalysis data did not reveal any treatment-related abnormalities. Monthly intradermal skin sensitization test results did not show any cell-mediated or delayed hypersensitivity reactions. Two animals developed low titers of antibodies to Synvisc® (possibly due to contamination by gram-negative bacterial lipopolysaccharide), while five animals developed antibodies to chicken proteins.

Four animals treated with Synvisc® died during this study. The death rate in the Synvisc® treated group did not exceed that for the remainder of the monkey colony during this time period.

Clearance: The kinetics of the clearance of hylan A, hylan B, and Synvisc® were studied by injection of radiolabeled hylan A and/or hylan B into the knees of rabbits at therapeutic concentrations. The half-lives of the elimination of these materials were calculated from measurements of the material remaining in the synovial fluid at various times after injection; hylans adhering to tissue surfaces were considered part of an elimination compartment and were not included in the calculation of the half-lives. The clearance of Synvisc® was measured using Synvisc® made from a combination of radiolabeled hylan A and hylan B. There was no significant inhibition of the clearance of one component of Synvisc® by the other (Table 1).

The half-life of hylan A in the blood was measured in a competitive-binding radioimmunoassay after the injection of unlabeled hylan A into the auricular artery of rabbits at levels about 500 times that of the normal blood level. By this method, hylan A had a half-life in the blood of 16-17 minutes (Table 2). This is longer than the 3-5 minute physiological half-life in blood reported in the scientific literature for native hyaluronan (hyaluronic acid). The longer half-life of hylan A may reflect the higher molecular weight of the cross-linked hylan as compared to native hyaluronan.

The clearance of intravascular hylan B from the blood cannot be directly determined by intravascular administration because hylan B is an insoluble particulate gel. Therefore, unlabeled hylan B was degraded and solubilized by breaking glycosidic bonds with acid hydrolysis to produce hylan B polysaccharides, which can be injected intravascularly. These polysaccharides are similar to the solubilized form of hylan B which exists in the joint and which enters the blood stream after hylan B is injected into the joint and

degraded. Following intravascular injection, the half life in the blood of unlabeled soluble degraded hylan B was found to be 22 minutes (Table 2).

IX. SUMMARY OF CLINICAL INVESTIGATIONS

The safety and/or effectiveness of Synvisc® for the treatment of osteoarthritis (OA) of the knee were evaluated in seven clinical investigations conducted in three countries. The investigations had a total of 738 human subjects (Table 3). All of the investigations were performed in accordance with the Declaration of Helsinki and/or with Good Clinical Practice guidelines.

Six double-blind studies (Studies #1, #2, #3, #5, #6 and #7) compared Synvisc® to a control treatment (intra-articular saline, hyaluronan or nonelastoviscous hylan fluid, or arthrocentesis). Control subjects in Study #6 received NSAID therapy as well as arthrocentesis.

Study #5, conducted in the U.S.A. under IDE #G890108, evaluated the safety and effectiveness of a single course three Synvisc® injections as well as the safety of a second course of Synvisc® treatment. The study contained an alternative treatment (arthrocentesis) for the first course of Synvisc®, but did not contain a concurrent control group for the second course of Synvisc®.

Study #4 was intended to evaluate the safety of Synvisc® without a comparison to an alternative treatment. All subjects in this study received Synvisc®.

All but two of the trials (Studies #1 and #2) were conducted at more than one investigational site.

Clinical Investigation Methodology

Subject Population: All subjects participating in the seven clinical studies had chronic idiopathic osteoarthritis of the knee with moderate to severe pain. Most of the studies limited enrollment to subjects with Grade I to Grade III radiological changes of the study knee, but three studies, #4, #5 and #7, included subjects with Grade IV X-rays.

Subjects were excluded from all studies if they had been diagnosed with rheumatoid arthritis, arthritis of metabolic origins or chondromalacia or had been treated with arthroscopy within two months or with intra-articular steroid within three months of the beginning the study. Subjects were also excluded if they were limited in their daily activities because of disorders other than OA of the knee, if they were taking steroid therapy, or if they were pregnant. In five studies, subjects were excluded if they had effusions in the joints of their treated knees.

A total of 738 subjects were enrolled in these studies. Ninety-five percent of the Synvisc®-treated subjects and 98% of controls completed the studies. A total of 511 subjects were treated with 1,771 Synvisc® injections.

Table 4 summarizes the demographic and disease characteristics of the subjects in these seven clinical trials. The majority of subjects had mid-stage X-ray grades (76% of subjects had Grades II and III on the Larsen or Kellgren-Lawrence scales) and had a disease duration of between one and five years (48%).

Effusion

Two studies (#5 and #6) contained subjects who presented with an effusion (34% of the subjects in Study #5 and 15% of the subjects in Study #6). If an effusion was present before any treatment or control injection, it was removed as completely as possible before the injection. Studies #1, #2, #3, #4 and #7 excluded subjects who had an effusion in the knee joint prior to the first intra-articular treatment in that knee.

Alternative Treatments (Controls)

All subjects participating in these studies received arthrocentesis with removal of effusion, if present. All subjects received either Synvisc® or one of three types of alternative (control) treatments.

In Studies #1, #2, and #3, the alternative treatment consisted of arthrocentesis followed by intra-articular injection of 2 ml phosphate-buffered saline solution, the solvent for Synvisc®. In Studies #5 and #6, nothing was injected into the control knees following arthrocentesis.

In Study #6, a group of control subjects received continued oral administration of an NSAID which had been well-tolerated by the subject for at least one month prior to the beginning of the study, but which had not provided adequate pain relief. Another group received Synvisc® as well as oral NSAIDs.

In Study #7, alternative-treatment subjects received one of three different nonelastoviscous hylan or hyaluronan preparations. Each of these preparations had lower elastoviscous properties than did Synvisc®.

Blinding

In studies #1, #2, #3, #5, #6 and #7, patients, injectors, and evaluators were blinded as to treatment. In Studies #5 and #6, where arthrocentesis alone was the only intra-articular treatment, a screen was set up so that the subject could not observe the procedure being performed.

Studies #1, #2, and #3 compared the results of injecting Synvisc® and saline intra-articularly in humans. To determine whether investigators could distinguish between these materials during the injection procedure, three separate studies were performed in which experienced and inexperienced blinded investigators injected one or both of the materials into the joints of rabbit knees. In all three animal studies, neither experienced nor inexperienced

injectors were able to differentiate between these two treatments while performing injections.

Pretreatment Medication

With the exception of Study #6, each of the five controlled clinical studies contained a "washout" period during which subjects withdrew from all anti-inflammatory medications before beginning intra-articular treatments. In Studies #1, #2, #3, #4 and #7, all subjects were required to discontinue all medication, including analgesics, during the two-week period immediately preceding the first intra-articular treatment.

In Study #5, subjects discontinued all anti-inflammatory medications for a four-week washout period preceding the first intra-articular treatment, but were permitted to take acetaminophen as an analgesic. Subjects in Study #6 did not discontinue their arthritis medications prior to Synvisc® treatment because the study was intended to evaluate Synvisc® therapy as a direct replacement for NSAID therapy.

Concomitant Medication and Rescue Therapy

In studies #1, #2, #3, #4, and #7 subjects were permitted to take any concomitant medications that they desired to treat their arthritis after treatment with the study medications had begun. All such medications were documented on the subjects' case report forms. Studies #5 and #6 permitted only the concomitant use of acetaminophen for analgesia.

In all studies, any concomitant medications taken by the subjects during the course of the trial were recorded, whether or not the medications were related to the subjects' arthritic pain. In studies #1, #2, #3, #4, and #7, concurrent therapies other than medications were not recorded. All concurrent therapies, including medications, physical therapy, and exercise, were recorded in Studies #5 and #6.

Subjects with Osteoarthritis in Both Knees

Subjects with OA in both knees were included in all seven studies. In Studies #4, #5 and #7, both knees of bilaterally affected subjects could be entered, treated and evaluated. In Study #6, only the most painful knee of bilaterally affected subjects was followed for the analysis of both safety and effectiveness. If the contralateral knee was painful, it could receive the same treatment as the target knee, but was followed only for the analysis of safety. In Studies #1, #2, and #3, bilaterally affected subjects were permitted to be treated only in the most painful knee.

Outcome Measures

The primary outcome measures of effectiveness in all of the trials were the subjects' evaluations of pain on 0-100 mm horizontal visual analog scales (VAS). All of the studies measured movement-related pain, requesting evaluator and/or subject assessment of "pain with motion", "weight-bearing pain", and "pain while walking". All of the studies also measured subjects' overall evaluations, night pain, and restriction of activity.

Rest pain was measured in Studies #5 and #6. Except in Study #5, night pain and rest pain were not predominant symptoms at baseline.

Blinded evaluators also questioned the subjects about the subjects' pain and activity levels and marked the VAS accordingly. Based on this information and on the evaluators' overall assessments of the subjects' conditions, the evaluators also recorded on the VAS their impressions of treatment success.

Statistical Methods

For all statistical analyses, two-tailed tests were used with alpha = 0.05. Improvements from baseline were calculated for individual subjects. Least squares means were then calculated from the individual subject improvements and were used for comparisons between treatment groups. The statistical significance of improvements from baseline was calculated by paired t-test. Between-group comparisons of improvement from baseline were calculated by one-way ANOVA.

Repeated measures analyses were conducted, when appropriate, using PROC MIXED. These analyses used all evaluation visits occurring after completion of treatment. Covariates to be used for both the repeated measures analyses and ANOVA were selected by stepwise regression.

Pivotal Studies

Three clinical studies (Studies #2, #3 and #5) compared three weekly injections of Synvisc® with concurrent placebo control treatments (saline or arthrocentesis). FDA considered these three investigations to be the most important for the determination of device effectiveness.

Clinical Studies of Effectiveness

Studies #1 and #2: Single-Center Treatment Regimen Studies

The first two clinical studies compared a treatment regimen of two injections applied two weeks apart (Study #1) to a regimen of three injections applied weekly (Study #2) at a single center. Each study compared Synvisc® treatment to the corresponding regimen of saline injections.

Synvisc® treatment showed statistically significant superiority ($p < 0.05$) over saline treatment for the two biweekly and the three weekly treatment regimens from Week 3 or 4 through the final study visit at Week 12 for most outcome measures. Three weekly injections of Synvisc® were statistically superior to two biweekly injections of Synvisc® from Week 8 onward. Table 5 illustrates this superiority for the subject evaluation of weight-bearing pain.

Study #3: Synvisc® vs. Saline Control Multicenter Study

Study #3 was designed to provide a multicenter, randomized, controlled double-blind comparison of a single course of three weekly Synvisc® injections vs. the same regimen of saline injections.

Tables #6 and #7 compare the Synvisc® and saline groups throughout the study with respect to their improvement (in mm) for all subject-evaluated VAS outcome measures. Subjects in both the Synvisc® and saline groups significantly improved after the first injection. The superiority of the Synvisc® group over the saline group was statistically significant in a combined analysis of data from all outcome measures at Weeks 3, 8, and 12 (1, 6, and 10 weeks after the last injection) (Table 6) and for each of the individual outcome measures at Weeks 8 and 12 (Table 7).

Study #4: Open-Label Study

Study #4 was a multicenter open-label study designed primarily to assess product safety in over 200 subjects treated with three weekly injections of Synvisc®. Measurements of outcome measures for effectiveness were also performed on VAS to document changes in these measures as compared to baseline and to compare such changes among different subpopulations of patients. There were no comparable control groups or alternative treatments in this study.

All of the evaluated outcome measures showed improvements as compared to baseline measurements that had been made before treatment had begun. Subjects with X-ray Grade IV OA experienced improvements in their own assessments of weight-bearing pain as compared to baseline that were comparable to those improvements observed in subjects with less severe disease (Table 8).

Study #5: Evaluation Three Synvisc® Injections vs. Three Arthrocenteses Following a Four Week Washout Period and Evaluation of a Second Synvisc® Treatment

Study #5 was a multicenter, randomized, controlled double-blind trial designed to establish safety and effectiveness of Synvisc® treatment as compared to arthrocentesis alone following a four-week washout period during which subjects received no treatments for their disease. The four-week washout period was intended to determine the natural history of OA after potential investigational subjects had discontinued all therapies for OA.

At the end of the four week no-treatment period, subjects electing to enter the first treatment phase of this study received either three weekly Synvisc® injections or three weekly arthrocenteses as a control. All subjects were permitted to take acetaminophen as an escape medication for pain after treatment began if they so desired.

Subjects were evaluated to determine their responses to treatment four weeks after their first intra-articular injections (two weeks after their third and last injections). This was the last evaluation point before any subjects were permitted to enter a second treatment phase of this investigation.

Upon their request and fulfillment of entry criteria, subjects entered the second phase of this investigation and received a course of three Synvisc® injections four or more weeks after they had completed their first course of treatment. Subjects were allowed to enter the second phase whether their first course of treatment had consisted of Synvisc® or of arthrocentesis alone. Adverse events were evaluated during both treatment phases.

The second phase of this study did not contain a concurrent control group that received an alternative treatment to Synvisc®. The effectiveness of Synvisc® effectiveness was therefore not evaluated after the second course of treatment had begun.

Both the Synvisc® and the arthrocentesis-treated subjects improved significantly in all outcome measures ($p < 0.05$) as compared to baseline. Two weeks after the first treatment, subjects injected with saline showed a significantly greater improvement in night pain than did patients injected with Synvisc® ($p < 0.004$) (Table 10). However, no other statistically significant difference ($p > 0.05$) in improvement from baseline was found between the Synvisc® and arthrocentesis groups in any outcome measure at any time throughout the four week evaluation period of the first treatment phase of this study in the intent-to-treat population, whether the analyses were corrected for covariates (Table 9) or not (Table 10). Thus, Synvisc® was no more effective than arthrocentesis alone in this population.

In a retrospective analysis, a subpopulation of 31 "flare" subjects were identified who had appeared to have responded better to Synvisc® than to arthrocentesis alone during the first treatment phase. In these 31 subjects, motion pain or rest pain had increased more than 20 mm on the VAS during the four-week "no-treatment" period. The 15 Synvisc®-treated "flare" subjects exhibited significantly greater improvements in most outcome measures than did the 16 comparable subjects that had been treated only with arthrocentesis (Tables 11 and 12).

There were no unanticipated adverse events in the 35 subjects who received two courses of Synvisc® treatment. The incidence and types of adverse events were similar to those in 43 subjects whose Synvisc® injections followed treatments with arthrocentesis alone.

Study #6: NSAID Alone vs. Synvisc® + NSAID

Study #6 was a multicenter, randomized, double-blind controlled study designed to evaluate the effectiveness of Synvisc® treatment either as a replacement or as an addition to NSAID therapy in subjects whose NSAID therapy had not provided adequate pain relief during the 30 days prior to Synvisc® treatment. Upon entering the trial, subjects were randomized into one of three treatment groups:

- o continuation of NSAID therapy plus three weekly arthrocentesis (NSAID-only group)
- o discontinuation of NSAID therapy and replacement with three weekly Synvisc® injections (Synvisc®-only group)
- o continuation of NSAID therapy plus three weekly Synvisc® injections (Synvisc®-plus-NSAID group)

There was no "washout period" in this study, nor were any subjects treated with saline or arthrocentesis alone.

All subjects received arthrocentesis with removal of any effusions at each treatment visit. Subjects were evaluated at follow-up visits for up to twelve weeks after receiving the first treatment. The seven and twelve week evaluations occurred after the completion of treatment.

Subjects in all three treatment groups experienced significant decreases of pain from baseline. There were no statistically significant differences ($p < 0.05$) in the outcome measures between the three treatment groups after the completion of treatment, except that the subjects taking only Synvisc® experienced a greater improvement in night pain than did the subjects treated only with NSAIDs (Table 13).

The data showed that a course of three Synvisc® injections is as least as effective as a continuation of NSAID therapy plus arthrocentesis in subjects who had not obtained adequate pain relief with NSAIDs prior to entering the study. They also showed that the pain-relieving effect of three Synvisc® injections can last for 12 weeks and is at least as effective as an NSAID administered continuously over the same 12-week period. A combination of the of the two treatments was no more or less effective than either one alone.

All subjects received arthrocentesis, but none received arthrocentesis alone. Therefore, the study was unable to determine whether the observed improvements were due to arthrocentesis, escape medication (acetaminophen) and the natural course of OA, or whether they were due to treatment with Synvisc® and/or NSAIDs.

Study #7: Relationship of Effectiveness and Elastoviscosity (Clinical Study #7)

Clinical Study #7, a double-blind, multicenter study, compared four different preparations composed of hyaluronans or hylans to determine whether a correlation could be established between the elastoviscosity of these products and their clinical effectiveness. The following preparations were tested:

- Synvisc® (elastoviscous hylan)
- Degraded Synvisc® (nonelastoviscous hylan)
- 1% hyaluronan, average molecular weight 750,000
- 1% hyaluronan, average molecular weight 2,000,000

All preparations had similar polysaccharide structures and concentrations (1%), and differed only in their average molecular weights and therefore in their elastoviscosities. Synvisc® had the highest elasticity and viscosity of those substances tested.

All subjects received three weekly injections of a hylan or hyaluronan preparation following a two week period during which they received no arthritis treatments. No subjects were treated with either saline or with arthrocentesis alone.

Subjects treated with Synvisc® often showed greater improvements in pain scores than did subjects receiving the other three treatments. However, these were differences were often not statistically significant, and in some instances were minimal.

Synvisc® showed significantly greater improvements in most outcome measures than did three injections of the 750,000 molecular weight hyaluronan preparation. For subject evaluations of weight-bearing pain at Week 12, Synvisc®-treated subjects showed a mean improvement of 38 ± 4 mm on the VAS. This was a significantly greater improvement ($p = 0.03$) than that experienced by subjects treated with the 750,000 molecular weight hyaluronan.

However, subjects treated with nonelastoviscous hylan showed an improvement in subject-evaluated weight-bearing pain measure of 36 ± 4 mm. This improvement was not significantly different from that experienced by Synvisc®-treated subjects. Moreover, there were no significant differences between the improvements in the VAS for any outcome measures between the group treated with Synvisc® and the group treated with the 2,000,000 molecular weight hyaluronan preparation. This preparation has an elastoviscosity that is lower than that of Synvisc® but is higher than that of the 750,000 molecular weight hyaluronan. Comparison of the Synvisc® group with less elastoviscous hyaluronan and hylan preparations suggested that the effectiveness of these materials may be related to their viscosities and elasticities. However, the study did not conclusively demonstrate this relationship.

Gender Analysis:

The gender of subjects were reported in all studies. There appear to be no effects of gender on the safety and effectiveness of Synvisc®.

X. CONCLUSIONS DRAWN FROM THE STUDIES

These studies provide reasonable assurance of the safety and effectiveness of Synvisc® for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics (e.g., acetaminophen). These studies demonstrated that:

- in subjects with OA of the knee who lack intra-articular effusions, who have not responded adequately to previous arthritis therapies, and who have not received any therapies during the previous two weeks, three weekly intra-articular knee injections of Synvisc® reduce knee pain to a greater extent than do comparable injections of saline for up to twelve weeks following the beginning of treatment (Studies #2 and #3).

- three weekly injections of Synvisc® are more effective than two weekly injections of the product (Studies #1 and #2).

- under certain investigational conditions, treatment with Synvisc® is no more effective than arthrocentesis alone (Study #5).

- injections of Synvisc® do not interfere with the pain-relieving effect of arthrocentesis when prior NSAID treatment is continued in subjects who have not responded adequately to NSAIDs during the month before they receive Synvisc® or arthrocentesis (Study #6).

XI. PANEL RECOMMENDATIONS

On November 20, 1996, the Orthopedics and Rehabilitation Devices Advisory Panel recommended approval of Biomatrix Corp.'s PMA for Synvisc® subject to the following:

1. The device is for use in subjects who are resistant to treatment with analgesics and NSAIDs, for up to three injections given in one course of treatment,

2. Conduct a post-approval study or studies which will include parameters which were not available at that time. These parameters include: synovial fluid analysis, quality of life, walking time, height, weight, outcome measures, safety and effectiveness in comparison to NSAIDs, and long term effects of treatment on joints.

3. Conduct a post-approval study to include multiple courses of injection and studies relating to the development of hypersensitivity reactions and pathology of the joints and lymph nodes as available.

4. Perform pathological studies in the monkeys previously treated with Synvisc® after each monkey expires.

5. The data required further analysis and reanalysis. Reanalysis would include analysis of covariates.

6. Address the possible influence of residual formaldehyde used in manufacturing Synvisc® on the safety and effectiveness of the final product.

7. Address the adequacy of using of immunodeficient nude mice in preclinical toxicity studies.

XII. CDRH DECISION

On February 22, 1997, CDRH informed Biomatrix, Inc., that further information on the clinical studies was needed, including a covariate analyses of data, on Synvisc®'s formaldehyde content and the effects of the formaldehyde on Synvisc®'s safety and effectiveness, and on the adequacy of using immunodeficient mice in its toxicity studies.

Biomatrix, Inc., responded satisfactorily to these concerns. Biomatrix, Inc., additionally agreed to perform pathological studies on each of the monkeys previously treated with Synvisc® after each animal expires.

CDRH did not agree with the advisory panel's recommendation that post-approval studies were needed to determine the safety and effectiveness of Synvisc® for the above indication, as CDRH considered that Biomatrix, Inc., had already provided sufficient data to support the indication.

CDRH did not agree with the advisory panel's recommendation that OA subjects must have failed to respond to NSAID therapy before receiving Synvisc®, since treatment with Synvisc® does not appear to be associated with the adverse gastrointestinal reactions (bleeding, nausea, etc.) that are known to occur with NSAIDs.

On August 8, 1997, CDRH approved a single course of three intra-articular Synvisc® injections for the treatment of pain in OA of the knee in subjects who have not responded adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen).

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling.

Postapproval Requirement and Restrictions: See approval order.

XIV. REFERENCES

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TABLE 1

Intra-Articular Clearance Studies in Rabbits

Test Article		Half-Life
[^{3}H]-hylan A fluid (1%) (avg. MW: 6 million)		1.2 ± 0.1 days
[^{3}H]-hylan B gel (0.4%)		7.7 ± 1.0 days
[^{3}H]/[^{14}C]-Synvisc®	^{14}C-hylan A fluid	1.5 ± 0.2 days
	^{3}H-hylan B gel	8.8 ± 0.9 days
Hyaluronan 1% (avg. MW: 1.7-2.6 million)[1]		11 hours

[1] Reference: Denlinger, 1982

TABLE 2

Clearance of Hylan A and Hylan B From Blood

Test Article	Dose (mg/kg)	Blood Half-Life (minutes)	% Cleared in 60 Minutes	Clearance Rate[1] (mg/kg/day)
hylan A	0.35[2]	16	96%	15.9
hylan A	0.67[2]	17	81%	28.5
hylan B[4]	23.7[3]	22	96%	77.4

1 daily clearance rates were calculated from the dose injected and the measured clearance rates (half-lives)

2 test species is New Zealand rabbit, assumes 3 kg. total body weight

3 test species is Sprague-Dawley rat, assumes 200g body weight

4 soluble degraded hylan B

TABLE 3

Description of the Clinical Trials Evaluating the Safety and Effectiveness of Synvisc®

Study No.	Description	Country	Number of Subjects
1	Double-blind comparison of the safety and effectiveness of two Synvisc® injections 14 days apart vs. the corresponding regimen of saline injections	Germany	48
2	Double-blind comparison of the safety and effectiveness of three weekly Synvisc® injections vs. the corresponding regimen of saline injections	Germany	30
3	Double-blind comparison of the safety and effectiveness of three weekly Synvisc® injections vs. the corresponding regimen of saline injections	Germany	110
4	Evaluation of the safety of three weekly Synvisc® injections and comparison of effectiveness in subpopulations; no control group	Germany	222
5	Double-blind comparison of the safety and effectiveness of three weekly Synvisc® injections vs. the corresponding regimen of arthrocenteses, with a four-week pretreatment medication washout period and an evaluation of the safety of a second course of Synvisc® treatment	U.S.A.	94
6	Double-blind comparison of the safety and effectiveness of three weekly Synvisc® injections with and without concomitant NSAID therapy vs. NSAID therapy with the corresponding regimen of arthrocenteses	Canada	102
7	Double-blind comparison of the effectiveness of three weekly injections of Synvisc® and of three other hyaluronan and hylan preparations vs. the relative elastoviscosities of the preparations	Germany	132

TABLE 4

Demographic Analysis of the Study Population for the Seven Clinical Studies

Male	296	(40%)
Female	442	(60%)
Age (yrs.)	61.3 ± 0.5[1]	
X-Ray Grade[2]		
I	96	(12%)
II	302	(38%)
III	305	(38%)
IV	95	(12%)
Disease Duration		
Mean (yrs)	6.0 ± 0.2	
<1 yr	122	(15%)
1-5 yrs	384	(48%)
>5 years	288	(36%)

[1] Mean ± Standard Error of Mean
[2] X-ray grade on Larsen or Kellgren-Lawrence scales

TABLE 5

Studies #1 & #2

Treatment Regimen Comparison of Weight-Bearing Pain

One-Way Analysis of Variance

Time (Weeks)	Saline Mean ± SEM[1] n = 39	Two Injections Mean ± SEM n = 23	Three Injections Mean ± SEM n = 15	*p-value*		
				Control vs. Two Injections	*Control vs. Three Injections*	*Two Injections vs. Three Injections*
0*	68 ± 3	61 ± 4	65 ± 5	*0.1*	*0.5*	*0.5*
1*	64 ± 4	NA[2]	54 ± 4	*NA*	*0.06*	*NA*
2*	47 ± 4	41 ± 5	34 ± 6	*0.4*	*0.06*	*0.3*
3	44 ± 5	NA	22 ± 5	*NA*	***0.004***	*NA*
4	47 ± 5	32 ± 5	NA	***0.02***	*NA*	*NA*
8	48 ± 4	32 ± 5	13 ± 6	***0.006***	***0.0001***	***0.01***
12	49 ± 4	27 ± 5	11 ± 6	***0.0003***	***0.0001***	***0.03***

[1] Mean ± SEM = Mean (mm) ± Standard error of mean on 100 mm VAS (raw scores)
* Injection Date
[2] NA = Not Applicable

TABLE 6

Study #3

Improvements from Baseline (Weeks 3, 8 and 12)

Patients ≥ 40 Years of Age

Repeated Measures Analysis (PROC MIXED)

Outcome Measure	Covariates[1]	Synvisc® Mean[2] ± SEM[3] N = 52	Saline Mean ± SEM N = 57	*p-value between treatments*
Patient evaluated weight-bearing pain	Center, baseline, age, x-ray grade and any concurrent therapy	39 ± 3	15 ± 3	***0.0001***
	p-value from baseline	***0.0001***	***0.0001***	
Patient evaluated night pain	Baseline, gender and any concurrent therapy	24 ± 2	14 ± 2	***0.001***
	p-value from baseline	***0.0001***	***0.0001***	
Patient assessment most painful knee movement	Center and concurrent therapy-NSAIDs	61 ± 4	33 ± 4	***0.0001***
	p-value from baseline	***0.0001***	***0.0001***	
Patient assessment success of treatment	Center, age, any concurrent therapy, x-ray grade and concurrent therapy -NSAIDs	69 ± 4	39 ± 4	***0.0001***
	p-value from baseline	***0.0001***	***0.0001***	
Evaluator assessment decrease of activity during daily chores	Center, baseline, age, x-ray grade and any concurrent therapy	33 ± 3	14 ± 2	***0.0001***
	p-value from baseline	***0.0001***	***0.0001***	

[1] The analyses were corrected for all covariates found to be statistically significant by stepwise regression. Each significant covariate is listed in the table with the individual outcome measure.

[2] Mean of assessments on VAS of 0 to 100 mm

[3] SEM = Standard Error of the Mean

TABLE 7

Study #3

Improvements from Baseline (Weeks 1 – 12)

Patients ≥ 40 Years of Age

Analysis of Variance[1]

	Baseline Mean[2] ± SEM[3]	Improvement (Change from Baseline) Mean ± SEM				
Week	0	1	2	3	8	12
Patient evaluated weight-bearing pain						
Synvisc®-treated	69.7 ± 2.3	12.0 ± 1.8	26.5 ± 2.5	37.9 ± 3.2	45.9 ± 3.2	46.5 ± 3.5
p-value from baseline	*NA[4]*	***0.0001***	***0.0001***	***0.0001***	***0.0001***	***0.0001***
Saline-treated	75.1 ± 2.3	9.0 ± 2.2	17.0 ± 2.3	23.0 ± 3.0	16.8 ± 4.0	16.4 ± 4.1
p-value from baseline	*NA*	***0.0001***	***0.0001***	***0.0001***	***0.0001***	***0.0002***
p-value between treatments	*0.1*	*0.3*	***0.01***	***0.0008***	***<0.0001***	***<0.0001***
Patient evaluated night pain						
Synvisc®-treated	41.6 ± 4.0	9.2 ± 1.8	20.0 ± 2.7	26.4 ± 3.5	28.3 ± 3.4	29.8 ± 3.7
p-value from baseline	*NA*	***0.0001***	***0.0001***	***0.0001***	***0.0001***	***0.0001***
Saline-treated	45.7 ± 4.1	9.5 ± 2.3	15.2 ± 2.6	21.2 ± 3.1	18.4 ± 3.6	17.3 ± 3.8
p-value from baseline	*NA*	***0.0001***	***0.0001***	***0.0001***	***0.0001***	***0.0001***
p-value between treatments	*0.5*	*0.9*	*0.2*	*0.3*	***0.05***	***0.02***
Patient assessment most painful knee movement						
Synvisc®-treated	NA	36.8 ± 4.0	44.7 ± 4.0	57.9 ± 3.8	71.5± 3.5	72.6 ± 4.0
p-value from baseline	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Saline-treated	NA	30.2 ± 3.8	31.4± 3.4	38.9 ± 3.6	38.1 ± 4.2	38.8 ± 4.3
p-value from baseline	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
p-value between treatments	*NA*	*0.2*	***0.01***	***0.0004***	***<0.0001***	***<0.0001***

[1] No correction for covariates
[2] Mean of assessments on VAS of 0 to 100 mm
[3] SEM = Standard Error of the Mean
[4] NA = Not Applicable

TABLE 7 (continued)

Study #3

Improvements from Baseline (Weeks 1 – 12)

Patients ≥ 40 Years of Age

Analysis of Variance[1]

	Baseline Mean[2] ± SEM[3]	Improvement (Change from Baseline) Mean ± SEM				
Week	0	1	2	3	8	12
Patient assessment success of treatment						
Synvisc®-treated	NA[4]	44.6 ± 4.8	59.6 ± 4.3	69.8 ± 3.7	78.9 ± 3.2	81.2 ± 3.3
p-value from baseline	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Saline-treated	NA	39.4 ± 4.2	41.8 ± 4.3	46.7 ± 4.2	43.6 ± 4.4	42.3± 4.5
p-value from baseline	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
p-value between treatments	*NA*	*0.4*	***0.005***	***0.0001***	***<0.0001***	***<0.0001***
Evaluator assessment decrease of activity during daily chores						
Synvisc®-treated	60.2 ± 3.1	11.2 ± 1.7	22.3 ± 2.4	31.1± 2.9	37.3 ± 3.1	37.6 ± 3.4
p-value from baseline	*NA*	***0.0001***	***0.0001***	***0.0001***	***0.0001***	***0.0001***
Saline-treated	68.0 ± 3.2	8.0 ± 1.6	14.5 ± 2.0	17.4 ± 2.3	17.2 ± 3.2	15.0 ± 3.2
p-value from baseline	*NA*	***0.0001***	***0.0001***	***0.0001***	***0.0001***	***0.0001***
p-value between treatments	*0.08*	*0.2*	***0.01***	***0.0003***	***<0.0001***	***<0.0001***

[1] No correction for covariates
[2] Mean of assessments on VAS of 0 to 100 mm
[3] SEM = Standard Error of the Mean
[4] NA = Not Applicable

TABLE 8

Study #4

Improvements in Subjects' Assessments of Weight-Bearing Pain Following Synvisc® Treatment

Comparison of Improvements in Subjects With X-Ray Grades I-III Osteoarthritis and in Subjects With X-Ray Grade IV Osteoarthritis

One-Way Analysis of Variance[1]

Timepoint (Week)	Improvement Mean[2] ± SEM[3]		
	Grades I - III n = 210	Grade IV n = 42	*p-value*
1	11 ± 1	12 ± 3	*0.6*
2	21 ± 1	23 ± 3	*0.6*
3	29 ± 2	30 ± 4	*0.9*
8	34 ± 2	33 ± 4	*0.9*
12	35 ± 2	36 ± 4	*0.9*

[1] No correction for covariates
[2] Mean of assessments (in mm) on VAS of 0 to 100 mm at specified time points subtracted from the mean of assessments on VAS at Week 0.
[3] SEM = Standard Error of the Mean

TABLE 9

Study #5

Improvement from Baseline Four Weeks After First Injection

(Phase I Evaluation Point)

Intent-to-Treat Population

Patients ≥ 40 Years of Age

Analysis of Variance

Outcome Measure	Covariates[1]	Synvisc® Mean[2] ± SEM[3] N = 47	Arthrocentesis Mean ± SEM N = 46	*p-value between treatments*
Patient assessment walking pain	Baseline, body mass index, x-ray grade and duration of disease	19 ± 4	15 ± 4	*0.5*
	p-value from baseline	***0.0001***	***0.001***	
Patient assessment motion pain	Baseline, gender, and x-ray grade	20 ± 5	16 ± 5	*0.5*
	p-value from baseline	***0.0001***	***0.002***	
Patient assessment night pain	Center, baseline and x-ray grade	25 ± 4	23 ± 5	*0.7*
	p-value from baseline	***0.0001***	***0.0001***	
Patient assessment restriction of activity	Baseline and gender	14 ± 4	13 ± 4	*0.8*
	p-value from baseline	***0.001***	***0.005***	
Patient overall assessment arthritic pain	Center, baseline, age, x-ray grade and contralateral knee	20 ± 4	16 ± 4	*0.4*
	p-value from baseline	***0.0001***	***0.0003***	

[1] The analyses were corrected for all covariates found to be statistically significant by stepwise regression. Each significant covariate is listed in the table with the individual outcome measure.

[2] Mean of assessments on VAS of 0 to 100 mm

[3] SEM = Standard Error of the Mean

TABLE 10

Study #5

Improvement from Baseline During Phase I

Intent-to-Treat Population

Patients ≥ 40 Years of Age

Analysis of Variance[1]

	Baseline Mean[2] ±SEM[3]	Improvement (Change from Baseline) Mean ± SEM		
Week	0	1	2	4
Patient assessment walking pain				
Synvisc®-treated	78.1 ± 2.3	12.1 ± 3.0	18.5 ± 3.6	21.0 ± 4.3
p-value from baseline	*NA[4]*	***0.0002***	***0.0001***	***0.0001***
Saline-treated	80.1 ± 2.3	10.1 ± 3.4	23.7 ± 4.6	19.5 ± 4.6
p-value from baseline	*NA*	***0.004***	***0.0001***	***0.0001***
p-value between treatments	*0.5*	*0.7*	*0.4*	*0.8*
Patient assessment motion pain				
Synvisc®-treated	67.3 ± 2.4	12.9 ± 3.2	18.9 ± 3.8	21.3 ± 3.9
p-value from baseline	*NA*	***0.0002***	***0.0001***	***0.0001***
Saline-treated	69.4 ± 3.2	9.4 ± 3.6	21.2 ± 4.5	19.1 ± 4.7
p-value from baseline	*NA*	***0.01***	***0.0001***	***0.0002***
p-value between treatments	*0.6*	*0.5*	*0.7*	*0.7*
Patient assessment night pain				
Synvisc®-treated	61.0 ± 3.7	19.0 ± 3.9	17.9 ± 3.5	22.8 ± 4.5
p-value from baseline	*NA*	***0.0001***	***0.0001***	***0.0001***
Saline-treated	76.0 ± 3.0	23.3 ± 4.6	36.3 ± 5.2	29.8± 5.3
p-value from baseline	*NA*	***0.0001***	***0.0001***	***0.0001***
p-value between treatments	***0.002***	*0.5*	***0.004***	*0.3*

[1] No correction for covariates
[2] Mean of assessments on VAS of 0 to 100 mm
[3] SEM = Standard Error of the Mean
[4] NA = Not Applicable

TABLE 10 (continued)

Study #5

Improvement from Baseline During Phase I

Intent-to-Treat Population

Patients ≥ 40 Years of Age

Analysis of Variance[1]

	Baseline Mean[2] ± SEM[3]	Improvement (Change from Baseline) Mean ± SEM		
Week	0	1	2	4
Patient assessment restriction of activity				
Synvisc®-treated	69.2 ± 3.0	9.3 ± 3.1	10.7± 3.0	15.4 ± 3.5
p-value from baseline	*NA[4]*	***0.004***	***0.0009***	***0.0001***
Saline-treated	63.1 ± 4.0	9.5 ± 3.1	14.7 ± 4.8	15.6 ± 3.7
p-value from baseline	*NA*	***0.003***	***0.003***	***0.0001***
p-value between treatments	*0.2*	*1.0*	*0.5*	*1.0*
Patient overall assessment arthritic pain				
Synvisc®-treated	76.5 ± 2.2	12.8 ± 2.8	19.2 ± 3.4	21.4± 4.0
p-value from baseline	*NA*	***0.0001***	***0.0001***	***0.0001***
Saline-treated	78.0 ± 2.7	11.8 ± 3.4	23.8 ± 4.3	20.7 ± 4.6
p-value from baseline	*NA*	***0.0009***	***0.0001***	***0.0001***
p-value between treatments	*0.7*	*0.8*	*0.4*	*0.9*

[1] No correction for covariates
[2] Mean of assessments on VAS of 0 to 100 mm
[3] SEM = Standard Error of the Mean
[4] NA = Not Applicable

TABLE 11

Study #5

Improvement from Baseline Four Weeks After First Injection

(Phase I Evaluation Point)

Flare Population

Patients ≥ 40 Years of Age

Analysis of Variance

Outcome Measure	Covariates[1]	Synvisc® Mean[2] ± SEM[3] N = 14	Arthrocentesis Mean ± SEM N = 16	*p-value between treatments*
Patient assessment walking pain	Baseline, body mass index, x-ray grade and duration of disease	41 ± 5	13 ± 4	***0.0003***
	p-value from baseline	***0.0001***	***0.008***	
Patient assessment motion pain	Baseline, gender, and x-ray grade	34 ± 5	11 ± 5	***0.003***
	p-value from baseline	***0.0001***	***0.04***	
Patient assessment night pain	Center, baseline and x-ray grade	59 ± 8	26 ± 8	***0.005***
	p-value from baseline	***0.0001***	***0.003***	
Patient assessment rest pain	Center, baseline and x-ray grade	46 ± 5	19 ± 5	***0.0007***
	p-value from baseline	***0.0001***	***0.002***	
Patient assessment restriction of activity	Baseline and gender	23 ± 5	16 ± 4	*0.2*
	p-value from baseline	***0.0001***	***0.001***	
Patient overall assessment arthritic pain	Center, baseline, age, x-ray grade and contralateral knee	50 ± 7	18 ± 6	***0.0001***
	p-value from baseline	***0.0001***	***0.007***	

[1] The analyses were corrected for all covariates found to be statistically significant by stepwise regression. Each significant covariate is listed in the table with the individual outcome measure.

[2] Mean of assessments on VAS of 0 to 100 mm

[3] SEM = Standard Error of the Mean

TABLE 12

Study #5

Improvement from Baseline During Phase I

Flare Population

All Patients[1]

Analysis of Variance[2]

	Baseline Mean[3] ± SEM[4]	Improvement (Change from Baseline) Mean ± SEM		
Week	0	1	2	4
Patient assessment walking pain				
Synvisc®-treated	80.5 ± 3.7	23.7 ± 4.2	25.7 ± 5.8	34.4 ± 5.8
p-value from baseline	*NA[5]*	***0.0001***	***0.0001***	***0.0001***
Saline-treated	81.0 ± 3.5	7.1 ± 4.1	23.6 ± 5.6	18.3 ± 5.4
p-value from baseline	*NA*	***0.09***	***0.0002***	***0.002***
p-value between treatments	*0.9*	***0.009***	*0.8*	***0.05***
Patient assessment motion pain				
Synvisc®-treated	70.8 ± 4.7	23.5 ± 5.6	25.9 ± 6.3	37.5 ± 6.4
p-value from baseline	*NA*	***0.0002***	***0.0003***	***0.0001***
Saline-treated	66.9 ± 4.5	0.3 ± 5.4	18.1± 6.1	16.3 ± 6.0
p-value from baseline	*NA*	*1.0*	***0.006***	***0.01***
p-value between treatments	*0.6*	***0.006***	*0.4*	***0.02***
Patient assessment night pain				
Synvisc®-treated	67.2 ± 4.6	24.9 ± 7.3	26.7 ± 7.9	42.8 ± 8.0
p-value from baseline	*NA*	***0.002***	***0.002***	***0.0001***
Saline-treated	83.1 ± 4.5	19.4 ± 7.1	37.0± 7.7	21.7± 7.5
p-value from baseline	*NA*	***0.01***	***0.0001***	***0.007***
p-value between treatments	***0.02***	*0.6*	*0.4*	*0.06*

[1] One Synvisc® patient < 40 years old
[2] No correction for covariates
[3] Mean of assessments on VAS of 0 to 100 mm
[4] SEM = Standard Error of the Mean
[5] NA = Not Applicable

TABLE 12 (continued)

Study #5

Improvement from Baseline During Phase I

Flare Population

All Patients[1]

Analysis of Variance[2]

	Baseline Mean[3] ± SEM[4]	Improvement (Change from Baseline) Mean ± SEM		
Week	0	1	2	4
Patient assessment rest pain				
Synvisc®-treated	67.8 ± 5.7	19.6 ± 7.0	30.3 ± 7.6	41.1 ± 7.1
p-value from baseline	*NA[5]*	***0.009***	***0.0004***	***0.0001***
Saline-treated	66.0 ± 5.5	5.5 ± 6.8	21.7 ± 7.4	18.4 ± 6.7
p-value from baseline	*NA*	*0.4*	***0.006***	***0.01***
p-value between treatments	*0.8*	*0.2*	*0.4*	***0.03***
Patient assessment restriction of activity				
Synvisc®-treated	70.8 ± 6.5	13.2 ± 3.6	22.1± 6.2	25.6 ± 4.7
p-value from baseline	*NA*	***0.001***	***0.001***	***0.0001***
Saline-treated	68.6 ± 6.3	9.8 ± 3.5	21.9 ± 6.0	18.8 ± 4.4
p-value from baseline	*NA*	***0.009***	***0.001***	***0.0002***
p-value between treatments	*0.8*	*0.5*	*1.0*	*0.3*
Patient overall assessment arthritic pain				
Synvisc®-treated	77.3 ± 4.4	19.7 ± 4.4	30.6 ± 6.3	36.5± 6.6
p-value from baseline	*NA*	***0.0001***	***0.0001***	***0.0001***
Saline-treated	79.7 ± 4.3	8.5 ± 4.3	23.1 ± 6.1	17.9 ± 6.2
p-value from baseline	*NA*	*0.06*	***0.0007***	***0.007***
p-value between treatments	*0.7*	*0.08*	*0.4*	***0.05***

[1] One Synvisc® patient < 40 years old
[2] No correction for covariates
[3] Mean of assessments on VAS of 0 to 100 mm
[4] SEM = Standard Error of the Mean
[5] NA = Not Applicable

TABLE 13

Study #6

Improvements from Baseline (Weeks 7 and 12)

Patients ≥ 40 Years of Age

Repeated Measures Analysis (PROC MIXED)

Outcome Measure:	Covariates[1]	Synvisc® Mean[2] ± SEM[3] (n)	NSAIDs Mean ± SEM (n)	Synvisc® & NSAIDs Mean ± SEM (n)	*p-value between groups*		
					Synvisc® vs. NSAIDs	*Synvisc® & NSAIDs vs. NSAIDs*	*Synvisc® & NSAIDs vs. Synvisc®*
Motion Pain	Center, baseline, age, x-ray grade and duration of disease	27 ± 5 (26)	20 ± 4 (32)	23 ± 4 (33)	*0.2*	*0.6*	*0.4*
	p-value from baseline	***0.0001***	***0.0001***	***0.0001***			
Night Pain	Center, baseline and duration of disease	18 ± 3 (26)	11 ± 3 (32)	15 ± 3 (34)	***0.05***	*0.2*	*0.5*
	p-value from baseline	***0.0001***	***0.0001***	***0.001***			
Rest Pain	Baseline, duration of disease, contralateral knee and any concurrent therapy	17 ± 3 (26)	13 ± 3 (32)	16 ± 3 (34)	0.2	0.4	0.6
	p-value from baseline	***0.0001***	***0.001***	***0.0001***			
Restriction of Activity	Baseline, age, x-ray grade and duration of disease	16 ± 4 (26)	15 ± 4 (32)	13 ± 4 (33)	*0.9*	*0.7*	*0.6*
	p-value from baseline	***0.0004***	***0.0003***	***0.001***			
Pt. Evaluated Overall Pain	Baseline, age and duration of disease	27 ± 4 (26)	20 ± 4 (32)	21 ± 4 (34)	*0.2*	*0.8*	*0.3*
	p-value from baseline	***0.0001***	***0.0001***	***0.0001***			

[1] The analyses were corrected for all covariates found to be statistically significant by stepwise regression. Each significant covariate is listed in the table with the individual outcome measure.

[2] VAS in mm

[3] SEM = Standard Error of the Mean