SUMMARY OF SAFETY AND EFEFCTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Hyaluronic Acid, Intraarticular
Device Trade Name:	Synvisc-One™
Applicant's Name and Address:	Genzyme Corporation 55 Cambridge Parkway Cambridge, MA 02142
Date(s) of Panel Recommendation:	December 9, 2008
Premarket Approval Application (PMA) Number:	P940015/S012
Date of FDA Notice of Approval:	February 26, 2009

Expedited: NA

The original PMA application P940015 for Synvisc® (hylan G-F 20) was approved on August 8, 1997. That device is a three injection regimen which is indicated for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen). Preclinical data from the original application are applicable to the current PMA supplement for Synvisc-One™ (hylan G-F 20) and are therefore incorporated by reference. Please refer to the SSED for P940015 for additional supporting documentation. You may obtain a copy of the SSED via the CDRH website at http://www.fda.gov/cdrh/pdf/p940015b.pdf. Written requests for copies can be obtained from The Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857 under Docket # 98M-0217.

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Synvisc-One labeling.

V. DEVICE DESCRIPTION

Synvisc-One (hylan G-F 20) is an elastoviscous high molecular weight fluid containing hylan A and hylan B polymers produced from chicken combs. Hylans are derivatives of hyaluronan (sodium hyaluronate). Hylan G-F 20 is unique in that the hyaluronan is chemically crosslinked. Hyaluronan is a long-chain polymer containing repeating disaccharide units of Na-glucuronate-N-acetylglucosamine. The contents of the syringe are sterile and non-pyrogenic.

. Each syringe of Synvisc-One contains:

Hylan polymers (hylan A + hylan B)	**48 mg**
Sodium chloride	**51 mg**
Disodium hydrogen phosphate	**0.96 mg**
Sodium dihydrogen phosphate monohydrate	**0.24 mg**
Water for injection	**q.s. to 6.0 ml**

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies to Synvisc-One for the treatment of OA include non-drug treatments and alternative drug therapies. Non-drug treatments include avoiding activities that cause knee pain, exercise, physical therapy, weight loss and removal of excess fluid from the knee. Alternative drug therapies include the use of pain relievers, such as acetaminophen, drugs that reduce inflammation, such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, or other intra-articular (IA) injections of corticosteroids or injections of unmodified hyaluronan (sodium hyaluronate).

VII. MARKETING HISTORY

Synvisc-One has not been marketed in any country to date. Synvisc-One has not been withdrawn from marketing in any countries. Synvisc which is the same material as Synvisc-One, only in a 3-injection regimen rather than a single injection, has been commercially available for more than 10 years and is approved for sale in over 70 countries throughout the world.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with intra-articular (IA) joint injections, including IA injection of Synvisc-One:

- arthralgia
- arthritis
- arthropathy
- injection site pain
- joint effusion

There were also reports of the incidence of rash, hives, itching, fever, nausea, headache, dizziness, chills, muscle cramps, paresthesia, peripheral edema, malaise, respiratory difficulties, flushing and facial swelling.

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

IX. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of Synvisc-One for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics e.g., acetaminophen. Data from this clinical study were the basis for the PMA approval decision.

The study was a prospective, multi-center, randomized, double-blind, two-arm (parallel group) clinical study conducted at 21 sites in 6 European countries: Belgium, Czech Republic, France, Germany, the Netherlands and the United Kingdom, Two hundred fifty-three (253) patients were randomized to receive either a single intra-articular (IA) injection of Synvisc-One (n=124) or Phosphate buffered saline (PBS) (n=129) between May 2005 to September 2006 as part of this study. Neither the patients nor the clinical observers knew the patients' treatment allocations.

A. Study Design:

The study was conducted in two phases:

- An initial treatment phase to evaluate the safety and efficacy of a single IA dose of 6 mL of Synvisc-One injected into the knee from baseline through 26 weeks.
- An open-label repeat treatment phase of a second 6-mL injection of Synvisc-One 26 weeks after the initial treatment phase was also assessed for safety.

The study objective of the Initial Treatment Phase Study was to compare the safety and efficacy of 1 x 6-mL IA injection of Synvisc-One against 1 x 6-mL IA injection of control [phosphate-buffered saline (PBS)] in treating patients with symptomatic primary OA of the knee.

In addition, in order to assess the safety profile of a second repeat treatment, a second 6-mL injection of Synvisc-One 26 weeks after the initial treatment phase was also assessed at the 4 week time point. The primary objective of the Repeat Treatment Phase was to evaluate safety in patients receiving a second (repeat) IA treatment of 6mL of Synvisc-One at 26 weeks following the first course of treatment.

The study was designed as a superiority study comparing the safety and effectiveness of a single injection of Synvisc-One to the PBS control. The outcome measures collected included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; Likert 3.1 A version), patient global assessment (PTGA), clinical observer global assessment (COGA), and use of rescue analgesic (see Treatment and Evaluation Schedule). The intent-to-treat (ITT) population (all patients randomized) was used for the primary analysis. The primary efficacy analysis was a comparison over 26 weeks between the two treatment groups of change from baseline in the WOMAC A (Pain) Subscale (see Patient Population and Demographics), performed by analysis of covariance (ANCOVA).

1. Clinical Inclusion and Exclusion Criteria

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

All patients met the American College of Rheumatology (ACR) criteria for OA (Altman, 1986, Arthritis Rheum[1]). The main initial treatment phase inclusion criteria were the following:

- 40 years or older;
- Documented diagnosis of primary OA of the target knee;
- Radiographic evidence of OA in the tibio-femoral compartment of the target knee;
- Continued OA pain in the target knee despite conservative treatments;
- Score of 2 or 3 (0 to 4 scale) on WOMAC question A1 (pain while walking on flat surface); and
- A mean score of 1.5 to 3.5 on all five questions of the WOMAC subscale A (pain).

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

- Grade IV radiographic stage of the target knee according to the system of Kellgren and Lawrence (K-L) (Kellgren, 1957, Ann Rheum Dis [2]);
- Clinically apparent tense effusion of the target knee;
- Significant valgus/varus deformities;
- Viscosupplementation in any joint in the past nine months;
- Previous surgery at the target knee in the past six months;
- Symptomatic OA of the contralateral knee or either hip that is not responsive to acetaminophen; and
- Systemic or IA injection of corticosteroids in any joint within three months prior to screening.

Repeat Treatment Phase of the Study

After completion of all safety and efficacy assessments at the Week 26 visit, patients were offered participation in the Repeat Treatment Phase of the study, which lasted for an additional 4 weeks. Inclusion criteria (as described below) were assessed to determine whether the patient was eligible to receive a repeat course of Synvisc-One therapy. If the patient met these criteria, the injection was performed on the same day. All the patients were placed in the Synvisc-One treatment arm, regardless of their previous treatment allocation in the Initial Treatment Phase. The same rules and procedures regarding prohibited medications (as described below for the Initial Treatment Phase) continued to apply throughout the Repeat Treatment Phase.

Inclusion Criteria (for Repeat Treatment Phase):

Patients who completed the Week 26 assessments could be enrolled in the Repeat Treatment Phase of this study. To receive a repeat IA dosage of Synvisc-One (6mL) treatment during the Repeat Treatment Phase, patients were required to meet all of the following criteria:

- Must have continued to meet Screening Inclusion/Exclusion criteria
- Must have had no major safety concerns during the first course of treatment as assessed by the Investigator
- Must have had a WOMAC LK 3.1 A (Pain) score of at least 1
- Must, in the Investigator's clinical assessment, have been a candidate for treatment

- If female, must have had a negative urine pregnancy test and continued to use a medically acceptable form of contraception for the duration of the study. Otherwise, females were required to be surgically sterile, or postmenopausal (as documented in medical history) for at least 1 year.

2. Randomization

Once Baseline eligibility criteria were met, the patient was randomized to one of the following two groups:

- Group 1: Arthrocentesis followed by a 6-mL IA injection of Synvisc-One on Day 0
- Group 2: Arthrocentesis followed by a 6-mL IA injection of Placebo (PBS) on Day 0

The Blinded Evaluator and the patient were blinded to the treatment group assignment. Unblinded site personnel, such as the Unblinded Injector, were instructed not to reveal treatment group assignments to blinded personnel or to the patient to ensure that the blinding remained intact. Both study treatment administrations were to occur within the specified window (please refer to Table 4).

3. Screening Phase

At the Screening visit, patients underwent the informed consent process. After written informed consent was obtained, a Screening number was assigned and demographic data, height and weight, vital signs, medical history, and prior treatments and medications were obtained. A physical examination and radiographic assessment of the target knee (if no valid X-ray taken within 3 months prior to Screening was available) was performed. Radiographic assessment consisted of an anterioposterior (AP) view: weight bearing (extension or semi-flexion) profile and a femoro-patellar view at 30° classical.

The patient was instructed to begin the "washout" period of prohibited (pain and OA) medications (i.e., those with half-lives of > 5 hours); from that point forward, none of the prohibited medications were to be taken at any time during the study. Refer to Tables 2 and 3 for a listing of permitted and prohibited co-treatments and/or co-medications. The washout period lasted for up to 21 days, depending on the half-life of the medications. Baseline (Day 0) was scheduled between 2 and 21 days after Screening to allow for prohibited medication "washout" and patient scheduling. Adverse events (AEs) were collected and reported from the time the patient signed the informed consent until study completion.

4. Study Material Administration (Injection)

If a patient had clinically apparent tense effusion at the target knee at Baseline (following washout), he/she was considered a screen failure and may have been rescheduled to return to the site within the allowed time window and instructed by the site staff on how to prepare for the return visit. If at the time of the return visit, the patient still had clinically apparent tense effusion at the target knee, he/she was discontinued from study participation. If the tense effusion had resolved, the patient may have continued to participate in the study.

The IA injection of Clinical Trial Material (CTM) was administered by a qualified professional (Unblinded Injector) experienced in administering IA injections. The evaluator and the patient

were blinded to the treatment group assignment. The study treatment administration was to occur within the specified window.

5. Treatment Phase

For 48 hours prior to the Day 0 visit, patients were to forego those pain or OA medications that were otherwise permitted during the study (i.e., those with a half-life of ≤ 5 hours).

The patient's eligibility for participation in the study was re-evaluated at Baseline (Day 0) to confirm that the patient still met Screening eligibility criteria and that he/she adhered to the "washout" period, if required. In addition, each female patient had a urine pregnancy test, unless she was surgically sterile or postmenopausal (as documented in the medical history) for at least 1 year. AEs were recorded and any new medical findings and changes in medications or treatments were documented.

The patient completed patient questionnaires at Baseline (WOMAC LK 3.1, PTGA), and the Blinded Evaluator completed the COGA. The same Blinded Evaluator was to complete the COGA for a patient throughout the study. A mean score of 1.5 to 3.5 on the WOMAC LK 3.1 A (Pain) and a score of 2 or 3 on the WOMAC LK 3.1 A1 (Pain while walking on a flat surface) was required to qualify for the study.

6. Co-Treatments and/or Co-Medications

The protocol included specifics regarding the allowable and prohibited medications throughout the duration of the study. Tables 1 and 2 include a listing of permitted and prohibited co-treatments and/or co-medications throughout the study.

Table 1 Permitted Co-Treatments and/or Co-Medications:

Treatment &/or Medication Allowed	Restriction
Any treatment for a pre-existing condition or for an AE, outside of the study indication, that was not listed as prohibited.	Treatments could not be prohibited per protocol
Rescue medication for relief of target knee OA pain. Rescue medication was defined as paracetamol up to 4000 mg/day, and patients were instructed to discontinue its use 48 hours prior to a study visit	Rescue medication only, but not to exceed 4000 mg/day Not within 48 hours prior to study evaluation Patients were instructed not to take medications (other than rescue medications) for target knee OA pain relief
Low-dose aspirin (ASA), 325 mg or less per day, or other platelet aggregation inhibitors (e.g., clopidogrel)	Not to exceed 325mg/day
Other analgesics and analgesic doses of short-acting NSAIDs (with a half-life ≤ 5 hours) for indications other than OA	Not exceed recommended dosing in product information. Not taken for more than 5 consecutive days

pain at the target knee or post-injection local pain management, but not for more than 5 consecutive days or 10 days per month, and not within 48 hours prior to a study visit.	Not taken for more than 10 days/month Not within 48 hours prior to a study visit
Topical analgesics / NSAIDs for joints other than the target knee	Allowed at any site other than the target knee
Topical corticosteroids for skin irritations at any site except at target knee	Allowed at any site other than the target knee
Inhaled corticosteroids for pulmonary disease	None
Nonpharmacologic therapy (except physical therapy) for the lower extremities, if begun at least 1 month before Screening, not to be initiated or substantially altered during the study (except for discontinuation)	Allowable if started > 1 month before Screening, not to be initiated or substantially altered during the study except for discontinuation.
Nonpharmacologic therapy (e.g., physical therapy) for joints other than in the lower extremities, or other conditions	Allowed without restriction at any site other than the lower extremities
Assistive devices if used for 3 months or more prior to Screening, on the condition that they continued to be used throughout the study	Allowed if used > 3 months before Screening and continued to be used throughout the study
Glucosamine, chondroitin sulfate, diacerhein, or avocado/soya extracts started at least 2 months prior to Screening, not to be initiated or substantially altered during the study	Allowable if started at least 2 months before screening, not to be initiated or substantially altered during the study

Table 2. Prohibited Co-Treatments and/or Co-Medications:

Medications Not Allowed	Restriction
Analgesics or NSAIDs other than as described in permitted treatments (e.g., medications with a half-life > 5 hours were not permitted at any time during the study but rescue medications, and those with a half-life of ≤ 5 hours were permitted except in the 48 hours before a visit)	Beginning at Screening and lasting throughout the duration of the trial (or study discontinuation)
Chronic use of narcotics	
Systemic corticosteroid(s) (oral or injected)	
Systemic corticosteroid(s) (oral or injected)	
Local corticosteroid injection into any joint or periarticular structure in the lower extremities	
Any surgery of the target knee during the trial	
Heparin or anti-vitamin K (e.g., crystalline warfarin) anticoagulant therapy	
Viscosupplementation injected into any joint other than as required by the protocol	Within 3 months prior to Screening and lasting throughout the duration of the trial (other than as required by the protocol)
Any investigational drug, device or biologic used within 3 months prior to Screening and during the study (other than as required by the protocol)	Screening and lasting throughout the duration of the trial (or until study discontinuation)

The following concomitant treatments and/or medications were prohibited during the Initial Treatment Phase of the study:

- Analgesics or NSAIDs other than as described in permitted treatments (e.g., medications with a half-life > 5 hours were not permitted at any time during the study but rescue medications, and those with a half-life of ≤ 5 hours were permitted except in the 48 hours before a visit)
- Chronic use of narcotics
- Systemic corticosteroid(s) (oral or injected)
- Local corticosteroid injection into any joint or periarticular structure in the lower extremities

- Physical therapy for the lower extremities during the study and within a month prior to Screening
- Any surgery of the target knee during the trial
- Heparin or anti-vitamin K (e.g., crystalline warfarin) anticoagulant therapy
- Viscosupplementation injected into any joint other than as required by the protocol
- Any investigational drug, device or biologic used within 3 months prior to Screening and during the study (other than as required by the protocol)

7. Follow-up Schedule

All patients were to return for follow-up within specified visit windows at Day 0 (baseline) 1, 4, 8, 12, 18, and 26 weeks following injection as denoted in Table 4. For 48 hours prior to each visit, patients were to forego those pain or OA medications that were otherwise permitted during the study (i.e., those with a half-life of $\leq$ 5 hours). The site called each patient at 1-week intervals between scheduled visits in order to record data regarding concomitant medications. Data collected included the product name, the exact dose, the days of intake and the indication.

Safety and efficacy assessments were to be made at each patient visit according to the Schedule of Study Events provided in Table 3. Safety assessments included recording physical examination findings, urine pregnancy test results (for females of childbearing potential), concomitant medications and treatments to date, vital signs, and Adverse Events (AEs). The Blinded Evaluator was reminded to ask the patient if he/she experienced any AEs as a result of the injection. Only safety assessments (but not efficacy) were performed at Week 1.

Efficacy assessments included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC LK 3.1) for Pain score A, and subscore A1, Patient Global Assessment (PTGA), and Clinician Observer Global Assessment (COGA) questionnaires.

A target knee assessment was to be performed at every visit. At all follow-up visits after Week 1, the patient completed patient questionnaires (WOMAC LK 3.1 and PTGA). After the patient questionnaires were completed, the Blinded Evaluator completed the COGA (the same Blinded Evaluator was to complete the COGA for a patient throughout the study).

Concomitant medications and treatments, and AEs were recorded at all visits and any new medical findings and changes in medications were documented. Vital signs were obtained at Week 26. A physical examination and urine pregnancy test (if applicable) was performed at Week 26.

Any patient who discontinued the study prematurely after receiving at least one IA injection of either clinical trial material (CTM) was required to complete all final (Week 26) evaluations at the time of discontinuation.

Table 3. Schedule of Study Events

	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Visi7	Visit 8
	-21 days[8] to -2 days	Day 0	Week 1 (± 4days)	Week 4 (±4days)	Week 8 (± 7days)	Week12 (± 7days)	Week 18 (± 7days)	Week 26[9] (± 7days)
Informed Consent	X[4]							
Study Eligibility	X	X						X[10]
Demographics and	X							
Height and Weight	X							
Vital sign		X						X
Medical History	X							
Physical Examination								X
Target Knee	X	X	X	X	X	X	X	X
Pregnancy Test'		X[1]						X
Radiograph[2]	X[2]							
Prior Treatment and	X[3]							
Prohibited Medication	X[4]							
Rescue Medication		X	X	X	X	X	X	X
WOMAC		X		X	X	X	X	X
PTGA		X		X	X	X	X	
COGA[5]		X[5]		X[5]	X[5]	X[5]	X[5]	X[5]
OMERACT-OARSI				X[11]	X[11]	X[11]	X[11]	X[11]
Randomization[6]		X[6]						
Study Treatment		X						
AE Assessment	X	X	X	X	X	X	X	
Concomitant Treatment and Medications[3,7]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]

1. Only if female.
2. X-ray taken at Screening was only required if the patient had not had a valid X-ray taken within 3 months of study Screening
3. Including start/stop dates plus dose, route, and regimen for all medications.
4. Patients were consented prior to any study-specific procedures being performed including 'washout' of any including start/stop dates plus dose, route, and regimen for all medications.
5. The Blinded Evaluator's COGA assessment was performed following the patient's completion of questionnaires.
6. Patients were randomized to 1 of 2 study treatment arms: Synvisc-One or Placebo.
7. Concomitant treatments and medications were recorded at each site visit. The site called each patient at 1-week intervals between visits, to collect data on concomitant medications.
8. Screening may have occurred up to 21 days prior to Day 0, to allow for medication washout.
9. Any patients withdrawing prematurely were required to complete all (Week 26) assessments/procedures at the final visit.
10. For patients participating in the Repeat Treatment Phase, study eligibility was re-assessed at Week 26.
11. OMERACT-OARSI responder analysis:

Per the OMERACT-OARSI criteria, a patient is classified as a positive responder if at least one (1) of the following two (2) conditions is observed at the post-Baseline assessment:

- In either pain (WOMAC A subscore) or function (WOMAC C subscore), a high improvement in the subscore, where high improvement in a subscore is achieved if there is both a > 50% improvement from Baseline and an absolute change from Baseline of > 20 normalized units (NU),

OR

- Improvement in at least two (2) of the following three (3):

1. Improvement in pain (WOMAC A subscore) defined as > 20% improvement from Baseline and an absolute change from Baseline of > 10 NU
2. Improvement in function (WOMAC C subscore) defined as > 20% improvement from Baseline and an absolute change from Baseline of > 10 NU
3. Improvement in PTGA defined as > 20% improvement from Baseline and an absolute change from Baseline of > 10 NU

The Repeat Treatment Phase visit schedule and assessment collection consisted of 1 treatment administration visit and follow-up visits for safety at Repeat Weeks 1 and 4. In addition, the site called each patient at 1-week intervals between scheduled visits in order to record data regarding concomitant medications. Patients were free to withdraw consent and discontinue study participation at any time and without prejudice to further treatment. In addition, the patient's participation may have been discontinued at the discretion of the Investigator or the applicant at any time.

8. Prospective Endpoints

Safety:
Safety was determined using the incidence of treatment-emergent adverse events (AEs), vital signs, and physical examination findings. AEs were categorized using a standardized coding dictionary (e.g., Medical Dictionary for Regulatory Activities [MedDRA]).

Effectiveness Objectives:
Primary Efficacy Objectives:
To determine whether 1 x 6-mL injection of Synvisc-One provided superior pain relief (WOMAC LK 3.1 A) over 26 weeks as compared to a 1 x 6-mL IA injection of Phosphate-buffered saline (PBS) in treating patients with symptomatic primary OA of the knee.

Secondary Efficacy Objectives:

- To analyze the differences between the WOMAC A subscore from Baseline to the Week 26 assessment in the Synvisc-One treatment group and the Placebo group.
- To analyze the differences between the WOMAC A1 subscore over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc-One treatment group and the Placebo group.
- To analyze the differences between the WOMAC C subscore over 26 weeks and from Baseline tothe Week 26 assessment in the Synvisc-One treatment group and the Placebo group.
- To analyze the differences between the PTGA over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc-One treatment group and the Placebo group.
- To analyze the differences between the COGA over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc-One treatment group and the Placebo group.
- To analyze the differences between the percentages of positive responders to treatment for symptomatic primary OA of the knee over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc-One treatment group and the Placebo group (where response is defined with the OMERACT-OARSI set of responder criteria).

Success/Failure:
The criterion for success for this study was defined as a statistically significant overall difference between the Synvisc-One treatment group and the Saline Control group at the 5% significance level. Statistical inference was based on repeated measures of Analysis of Covariance (ANCOVA).

Statistical Considerations

Approximately 250 patients with symptomatic primary OA of the knee were planned to be randomized in the Initial Treatment Phase of the study. The sample size estimation was based on using the mean difference in the WOMAC LK 3.1 A change from Baseline in the primary efficacy analysis. The type I error rate was set at the 5% significance level for the primary efficacy analysis. All secondary effectiveness analyses were performed at the 5% significance level using a 2-sided type 1 error. No adjustment was made for multiple comparisons.

The primary efficacy analysis was performed on the intent-to-treat (ITT) population, which included all patients randomized, and was based on a repeated measures model that was used to test for differences in treatment efficacy, as quantified by the WOMAC LK 3.1 A subscore over 26 weeks between Synvisc-One and Placebo. The test of treatment efficacy was constructed using least-square mean estimates (linear combinations of the estimated regression parameters).

No interim analysis was performed for this study.

The safety analyses were performed on the Safety Population defined as all patients who underwent any study treatment. Treatment-emergent AEs were summarized by treatment group and categorized by severity and relationship to the study procedures. Treatment-emergent AEs were summarized both including and excluding AEs generated from deteriorations in the target knee assessment (if any). If a patient had more than 1 occurrence of the same AE, he/she was counted only once within that preferred term in the summary tables. The most severe occurrence of an AE, as well as the most extreme relationship of the AE to the study procedures and/or study treatment, was indicated in cases of multiple occurrences of the same AE. Target knee AEs also were summarized separately. No replacement on any missing or invalid data was made for the safety analyses.

For the Repeat Treatment Phase of the study, all treatment-emergent AEs were summarized.

B. Accountability of PMA Cohort:

A total of 253 patients were randomized to either receive Synvisc-One (124) or to receive PBS control (129) as part of the Initial Treatment Phase of the study.

There were 160 patients (Synvisc-One-Synvisc-One: 77 patients; Placebo-Synvisc-One: 83 patients) enrolled in the Repeat Treatment Phase (Safety) population.

Table 4 identifies patient dispositions at 6 months of the Intent-to-Treat (ITT) and per protocol populations (PPP) for the Initial Treatment Phase Study. Table 5 identifies patient dispositions at 4 weeks for the Repeat Treatment Phase of the study.

Table 4. Reasons Patients Were Ineligible for Per-Protocol Analysis – ITT Population

Category	Synvisc-One	Placebo	Total
Number of Patients in ITT Population, N	**124**	**129**	**253**
Number of Patients in the Per-Protocol Population, n (%)	**87 (70.2)**	**81 (62.8)**	**168 (66.4)**
Reason Patients in ITT Ineligible for Per-Protocol Analysis, n (%)			
Deviation From Visit Windows	**18 (14.5)**	**20 (15.5)**	**38 (15.0)**
Use of Prohibited Medications	**12 (9.7)**	**15 (11.6)**	**27 (10.7)**
Did not complete the study	**9 (7.3)**	**12 (9.3)**	**21 (8.3)**
Inclusion/Exclusion Criteria Not Met	**2 (1.6)**	**6 (4.7)**	**8 (3.2)**
Missing WOMAC, PTGA	**3 (2.4)**	**3 (2.3)**	**6 (2.4)**
Received Incorrect Kit	**1 (0.8)**	**1 (0.8)**	**2 (0.8)**

Note: Percentages are based on the number of patients in the ITT population, unless otherwise specified.
Note: Percentages for reasons for ineligibility are based on the number of patients in the ITT not in the Per-Protocol population.
Note: A patient may have had more than one reason for ineligibility for the Per-Protocol Population.

Table 5. Summary of Overall Patient Disposition by Treatment - Repeat Treatment Safety

Category	Synvisc One –Synvisc One* (n=123)	Placebo-Synvisc One* (n=130)	Total (n=253)
Number of Patients Eligible for the Repeat Treatment Phase, n(%)	**77 (62.6)**	**86 (66.2)**	**163 (64.4)**
Number of Patients in Repeat Safety Population, n (%)	**77 (62.6)**	**83 (63.8)**	**160 (63.2)**
Number of Patients, n (%)			
Completing the Phase	**77 (62.6)**	**81 (62.3)**	**158 (62.5)**

Not Completing Phase	0	2 (1.5)	2 (0.8)
Principal Reason for Withdrawal#, n (%)			
Adverse Experience	0	1 (50.0)	1 (50.0)
Non-compliant	0	0	0
Wishes to withdraw	0	0	0
Lost to Follow-up	0	0	0
Lack of Efficacy	0	0	0
Other	0	1 (50.0)	1 (50.0)

*: Treatment group reflects prior treatment. Patient 08009 received Placebo during Repeat Treatment and is not summarized. Treatment groups reflect the actual treatment received, not the randomized treatment.
#: Percentages for reasons for withdrawal of patients in Repeat Safety Population are based on the number of discontinued patients in the Safety Population.
Note: Percentages are based on the number of patients in Safety Population, unless otherwise specified.

C. Study Population Demographics and Baseline Parameters:

Study patients had primary OA of the knee per American College and Rheumatology criteria and were at least 40 years old. The diagnosis was confirmed via recent radiograph showing at least one osteophyte in the target knee. Study patients had continued target knee pain despite use of conservative treatment and NSAIDs. Patients with severe disease (Grade IV) per Kellgren-Lawrence criteria, or who had prior arthroplasty in the target knee[3], were excluded. At the beginning of the study, subjects had moderate or severe target knee pain when walking on a flat surface (on a 5-point Likert scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme), and an average score of 1.5 to 3.5 on the five questions of the WOMAC A (Pain) Subscale.

The WOMAC A Subscale asks study subjects to rate their degree of pain when:

- Walking on a flat surface
- Going up and down stairs
- Resting during the night
- Sitting or lying
- Standing upright

Tables 6 and 7 summarize the demographics and baseline characteristics for the Initial Treatment Phase of the study and for the Repeat Treatment Phase to assess safety, respectively. There were no clinically meaningful differences between treatment groups in any baseline parameter.

Table 6: Summary of Demographic and Baseline Characteristics – ITT Population

Parameter/Category	Synvisc-One (N=124)*	Saline Control (N=129)*	Total (N=253)
Age, n *	124	129	253
Mean (SD)	63.6 (9.6)	62.5 (9.2)	63.0 (9.4)
Range	42, 83	43, 84	42, 84
Sex, n *	124	129	253
Female, n (%)	92 (74%)	88 (68%)	180 (71%)
Race, n *	124	129	253
Caucasian, n (%)	118 (95%)	125 (97%)	243 (96%)
Non-Caucasian, n (%)	6 (5%)	4 (3%)	10 (4%)
Body Mass Index (kg/m2), n *	123	129	252
Mean (SD)	29.1 (4.8)	29.8 (5.7)	29.4 (5.3)
Range	20.7, 46.0	19.5, 52.4	19.5, 52.4
Prior Corticosteroids In Target Knee, n **	123	130	253
Yes – n (%)	40 (32%)	31 (24%)	71 (28%)
Prior Arthroscopy In Target Knee, n **	123	130	253
Yes – n (%)	26 (21%)	28 (22%)	54 (21%)
Tibio-Femoral Joint Modified Kellgren-Lawrence Numerical Grading System **			
Grade II	63 (51%)	51 (39%)	114 (45%)
Grade III	60 (49%)	78 (60%)	138 (55%)
Grade IV	0	1 (1%)	1 (0%)
Total WOMAC Score (0-96); Mean (SD) *	55.1 (10.5)	54.8 (9.4)	
WOMAC A Score (0-4); Mean (SD) *	2.30 (0.43)	2.25 (0.41)	
PTGA -- Mean (SD) (0-4) *	2.57 (0.67)	2.50 (0.64)	
COGA -- Mean (SD) (0-4) *	2.44 (0.76)	2.49 (0.75)	

* ITT Population
** Safety Population

Table 7. Summary of Demographic and Baseline Characteristics – Repeat Treatment Safety Population

	Synvisc-One-Synvisc-One* (N=77)	Saline-Synvisc One*(N=83)	Total (N=160)
Parameter/Category			
Age			
Mean (SD)	63.0 (9.47)	62.2 (9.49)	62.6 (9.46)
Median	63.0	62.0	62.0
Range	42, 83	43, 84	42, 84
Sex, n	77	83	160

Male, n (%)	**17 (22.1)**	**29 (34.9)**	
Female, n (%)	**60 (77.9)**	**54 (65.1)**	**114 (71.3)**
Race, n	**77**	**83**	**160**
Caucasian, n (%)	**74 (96.1)**	**81 (97.6)**	**155 (96.9)**
Black, n (%)	**3 (3.9)**	**1 (1.2)**	**4 (2.5)**
Hispanic, n (%)	**0**	**0**	**0**
Asian, n (%)	**0**	**1 (1.2)**	**1 (0.6)**
Other, n (%)	**0**	**0**	**0**
Weight (kg)			
Mean (SD)	**80.60 (15.183)**	**83.08 (16.346)**	**81.88 (15.796)**
Median	**79.00**	**0.00**	**79.50**
Range	**49.0, 132.9**	**56.7, 126.0**	**49.0, 132.9**
Height (cm)			
Mean (SD)	**165.6 (8.72)**	**166.9 (9.73)**	**166.3 (9.25)**
Median	**165.0**	**165.0**	**165.0**
Range	**145, 188**	**148, 191**	**145, 191**
Body Mass Index (kg/m2)			
Mean (SD)	**29.38 (5.109)**	**29.86 (5.644)**	**29.63 (5.382)**
Median	**29.00**	**28.65**	**28.66**
Range	**20.7, 46.0**	**20.9, 52.4**	**20.7, 52.4**

* Treatment group reflects prior treatment.

D. Safety and Effectiveness Results:

1. Safety Results

Adverse Events Involving the Injected Knee

A total of 253 (Synvisc-One: n=123, PBS Control: n=130) patients were treated in the study. Adverse Events (AEs) were collected and recorded from the time the patient signed the informed consent until study completion. The frequency and type of adverse events (AEs) were similar between the group of patients that received Synvisc-One and the group that received PBS injection.

Initial Treatment Phase:
The overall proportions of patients with Treatment-Emergent AEs regardless of device relatedness (Synvisc-One: n=70, 56.9%; PBS Control: n=79, 60.8%) and with target knee AEs regardless of device relatedness (Synvisc-One: n=44, 35.8%; PBS Control: n=44, 33.8%) were comparable between the two treatment groups (see Table 8). Table 9 lists the incidences of AEs in the target knee that were assessed by the applicant to be device related, defined as related to either the study injection or the study treatment.

Table 8: Patients with Adverse Events in the Injected Knee Regardless of Relatedness

MedDRA Preferred Term	Synvisc-One N=123 n (%)	Saline Control N=130 n (%)
Any Treatment-Emergent Adverse Event	44 (35.8%)	44 (33.8%)
Arthralgia	31 (25.2%)	28 (21.5%)
Joint stiffness	10 (8.1%)	13 (10.0%)
Joint effusion	7 (5.7%)	7 (5.4%)
Joint swelling	5 (4.1%)	7 (5.4%)
Joint warmth	2 (1.6%)	5 (3.8%)
Post-traumatic pain	0	3 (2.3%)
Injection site pain	1 (0.8%)	1 (0.8%)
Synovial cyst	0	2 (1.5%)
Arthritis	1 (0.8%)	0
Arthropathy	1 (0.8%)	0
Gait disturbance	1 (0.8%)	0
Joint range of motion decreased	0	1 (0.8%)
Osteoarthritis	0	1 (0.8%)

Note: Patients are counted once for each unique AE regardless of device relatedness, and may have had more than one unique AE

Table 9: Patients Device-Related Adverse Events in the Injected Knee

MedDRA Preferred Term	Synvisc-One N=123 n (%)	Saline Control N=130 n (%)
Any Device-Related Adverse Event	7 (5.7%)	4 (3.1%)
Arthralgia	2 (1.6%)	3 (2.3%)
Arthritis	1 (0.8%)	0
Arthropathy	1 (0.8%)	0
Injection site pain	1 (0.8%)	1 (0.8%)
Joint effusion	2 (1.6%)	0

Note: Patients are counted once for each unique AE and may have had more than one unique AE

Device-related AEs involving the injected knee were mild or moderate in nature and were treated symptomatically. There were no serious AEs in the injected knee in either the Synvisc-One or the PBS control group.

Repeat Treatment Phase:
The repeat treatment phase confirmed the safety profile of the initial phase with no increase of AEs in patients receiving a second injection of Synvisc-One. One hundred and sixty patients were treated during this phase of the study, of which 77 patients received a second injection of Synvisc-One. Of these 77 patients, 4 (5.2%) experienced five device-related AEs in the injected knee. All such events were mild to moderate and were treated symptomatically. These events were arthralgia (n=2), arthritis (n=1), injection site hematoma (n=1) and injection site pain (n=1). Patients who developed target knee AEs during the initial phase of the study and who subsequently received repeat treatment did not experience target knee AEs upon repeat exposure to Synvisc-One.

Overall Target Knee Safety Summary:
The safety profile of Synvisc-One is similar to the Clinical and Post-marketing experience seen with Synvisc® (3 injection regimen) where pain, swelling and effusion were the most frequently occurring AEs in the injected knee. There have been post marketing reports for Synvisc indicating that in some cases the joint effusion may be large and can cause pronounced pain; it is important to remove and to analyze the fluid to rule out infection or crystalline arthropathies. These types of severe AEs were not observed in either the initial or repeat treatment phase of the Synvisc-One study. Joint infections did not occur in any of the clinical studies of Synvisc or Synvisc-One and have been reported only rarely during clinical use of Synvisc.

Adverse Events Outside of the Target Knee:
Overall 101 patients (Synvisc-One: n=47, 38.2%; PBS Control: n=54, 41.5%) experienced at least one AE outside the target knee irrespective of device relatedness. The most commonly occurring (5% or greater in either group) AEs outside the target knee were headache, back pain, nasopharyngitis, and influenza. In the Synvisc-One group there was one AE of syncope considered device related. Synvisc® (3 injection regimen) post-marketing experience has identified the following systemic events to occur rarely with administration: rash, hives, itching, fever, nausea, headache, dizziness, chills, muscle cramps, paresthesia, peripheral edema, malaise, respiratory difficulties, flushing and facial swelling. There have been rare reports of thrombocytopenia coincident with Synvisc injection.
No new systemic AEs were identified during this study as compared to Synvisc®.

2. Effectiveness Results
The primary efficacy endpoint for the study, the difference between the treatment groups in Change from Baseline over 26 Weeks in the WOMAC A Pain Score (Table 10) was met, with the p-value of 0.047.

Table 10: Primary Efficacy Results: WOMAC A (Pain) Score Overall Change from Baseline Over 26 Weeks – ITT Population

	Baseline Mean (SE) (0-4 Scale)	Mean Post-treatment (SE) (0-4 Scale)	Estimated Change (SE) (0-4 Scale)	Estimated Difference from Saline Control (95% CI)	p-value (ANCOVA)
Synvisc-One (n=124)	2.30 (0.04)	1.43 (0.06)	-0.84 (0.06)	-0.15 (-0.302, -0.002)	0.047
Saline Control (n=129)	2.25 (0.04)	1.59 (0.06)	-0.69 (0.06)		

WOMAC A scale using 5 Liikert scale, where 0=no pain and 4 =extreme pain

Repeated measure Analysis of Covariance was used for the WOMAC A pain reduction score change from the baseline.

Synvisc-One also demonstrated statistically superiority to saline control in for several pre-defined secondary outcome measures, which included PTGA over and at 26 weeks, COGA over and at 26 weeks, and pain while walking on a flat surface (WOMAC A1) both over 26 weeks and at 26 weeks (see Table 11).

Table 11: Secondary Efficacy Endpoints

	Odds Ratio Generalized Estimating Equation for categorical data.		Definition	Explanation
WOMAC A1	Over 26 weeks	0.64*	The odds(probability(Worse)/Probability((Better)] for Synvisc-One for over 26 weeks and at 26 weeks is approximately 64%, and 56%, respectively, to the odds for control.	Synvisc-One patients were 1.56 times more likely to self-report pain relief while walking on a flat surface compared to those patients treated with saline control over 26 weeks and 1.79 times more likely to self-report pain relief while walking on a flat surface compared to those patients treated with saline control at 26 weeks.
	At week 26	0.56*		
PTGA	Over 26 weeks	0.69*	The odds [(probability(Worse)/Probability((Better)] for Synvisc-One for over 26 weeks and at 26 weeks is approximately 69%, and 51%, respectively, to the odds for control. PTGA: Patient Global Assessment has 5 scales (Very well, Well, Fair, Poor, Very poor)	Synvisc-One patients were 1.45 times more likely to self-report improvement in overall health status compared to those patients treated with saline control over 26 weeks and 1.96 times more likely to self-report improvement in overall health status compared to those patients treated with saline control at 26 weeks.
	At week 26	0.51*		
COGA	Over 26 weeks	0.71*	The odds [(probability(Worse)/Probability((Better)] for Synvisc-One for over 26 weeks and at 26 weeks is approximately 71%, and 56%, respectively, to the odds for control. COGA: Clinical Observer Global Assessment has 5 scales (Very well, Well, Fair, Poor, Very poor)	Blinded clinical observers were 1.41 times more likely to assess patients treated with Synvisc-One as showing overall improvement in disease status compared to those patients treated with saline control over 26 weeks and 1.79 times more likely to assess patients treated with Synvisc-One as showing overall improvement in disease status compared to those patients treated with saline control at 26 weeks.
	At w eek 26	0.56*		
OMERACT-OARSI Responder	Over 26 weeks	0.66	This responder effect did not reach statistical significance between the treatment groups.	
	At week 26	0.69		
Estimate of Treatment Difference (Analysis of Covariance)				
WOMAC C	Over 26 weeks	-0.18	The study did not show a statistically significant difference in functional improvement between the treatment groups.	
	At week 26	-0.11		

* Statistically significant at the 5% significance level; not adjusted for multiplicity

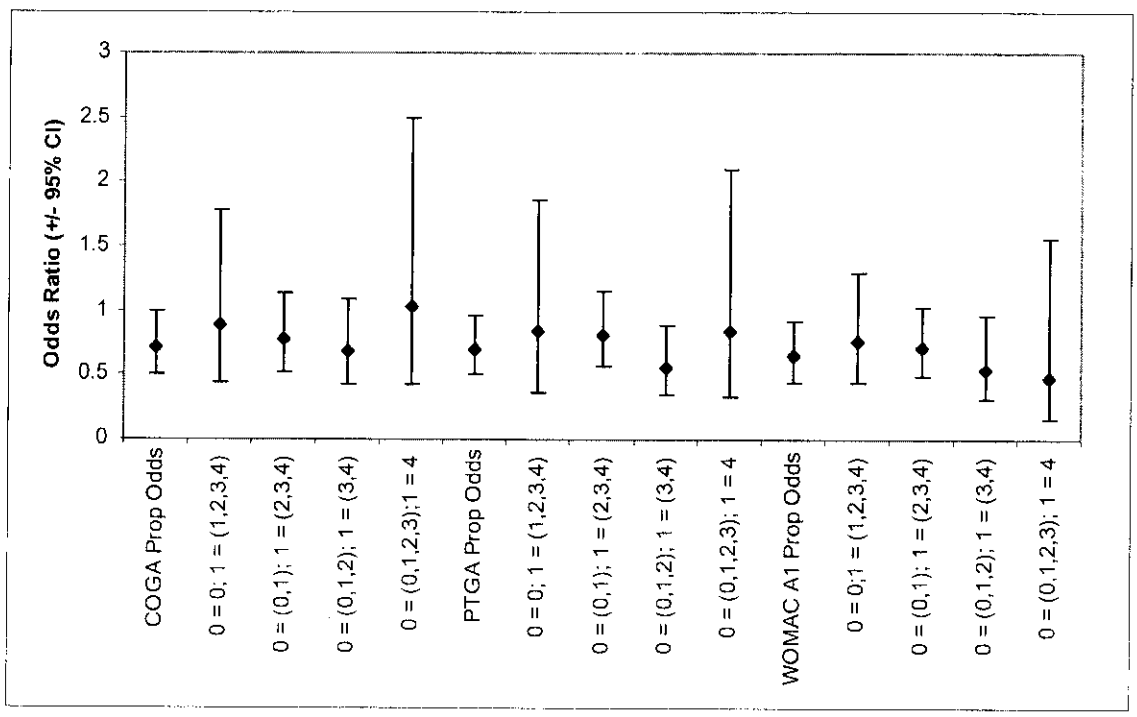
1Odds ratio = Odds for Synvisc-One/Odds for Control
= Prob [(Worse)/Probability(Better) for Synvisc-One] / [Prob (Worse)/Probability(Better) for Control].

If odds ratio < 1, then in favor of Synvisc-One

Use of a proportional odds model can produce a single summary measure of efficacy in the context of repeated measures ordered multinomial data. The proportional odds model assumes that comparisons between the treatment groups via the odds ratio are invariant as to how 'success' is defined. While formal testing of the proportional odds assumption is not available, logistic regression with GEE can be used for each of the 4 definitions of 'success'. As shown in the Figure 1 below, the estimated odds ratios from the individual logistic regressions are relatively consistent with the estimated proportional odds ratio; all of the 95% confidence intervals from the logistic regression models overlap with each other and with the proportional odds ratio confidence interval.

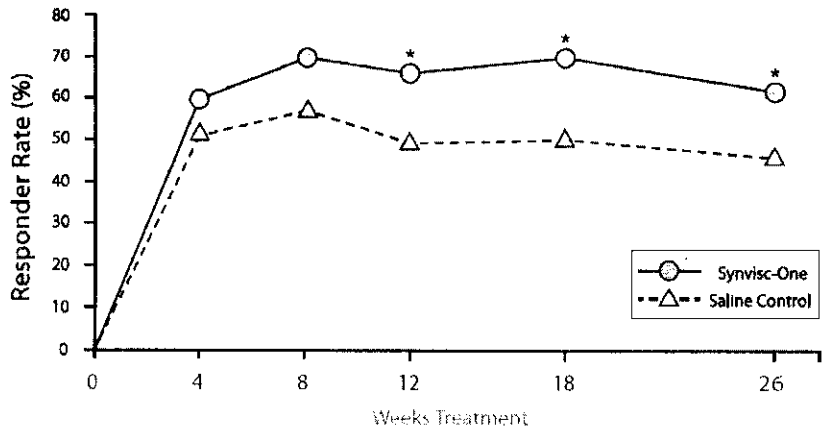
The proportional odds assumption was explored for the WOMAC A1, PTGA and COGA endpoints. For each of these endpoints, the proportional odds assumption appeared tenable and, therefore, inference is based on the proportional odds ratio (Figure 1).

Figure 1. Plot for Categorical Secondary Endpoints - ITT Population



The WOMAC A1 responder rate (where response was defined as a 1-or-more category improvement from baseline and the patient did not withdraw from the study) was significantly higher in the Synvisc-One group than in the saline control group. Seventy-one percent (71%) of the patients were responders at week 18 in the Synvisc-One group (versus 54% in the saline control group, p=0.003). At week 26, 64% of patients in the Synvisc-One group were responders, while only 50% of patients in the saline control group were responders (Figure 2).

Figure 2: Patient Responder Rate on WOMAC A1 (Walking Pain):



Note: Analyzed using generalized estimating equations (GEE) for binary outcomes
* Statistically significant at the 5% significance level; not adjusted for multiplicity

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

A. Panel Meeting Recommendation

At an advisory meeting held on December 9, 2008, the Orthopedics and Rehabilitation Devices Panel recommended that the Genzyme Biosurgery's PMA/Supplement for a single injection regimen of Synvisc-One be approved. This decision was based on the results of the pivotal study data presented. The following link contains the panel transcript for Synvisc-One: http:// www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4404-003.pdf). The Panel did not have any specific conditions of approval.

B. FDA's Post-Panel Action

There is neither pending nor outstanding issues. FDA concurs with the recommendation of the Orthopedics and Rehabilitation Devices Panel held on December 9, 2008, that Synvisc-One is reasonably safe and effective.

XI. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The adverse events rates between the Synvisc-One and saline control are comparable to each other. The device does not increase the adverse events, compared with the saline control group. No new systemic adverse events were identified during this study as compared Syvisc (3 injection regimen).

The repeat treatment phase confirmed the safety profile of the initial phase with no increase of AEs in patients receiving a second injection of Synvisc-One. There was a similar safety profile for Synvisc-One and saline control. No new unrecognized AE(s) were identified with a single injection of 6 mL of Synvisc-One during this study as compared to the currently approved multiple injection regimen.

The safety profile from the Initial Treatment Phase of the study was demonstrated during the Repeat Treatment Phase of the study, indicating no increase of AEs in the patients receiving a second 6 mL injection of Synvisc-One after 26 weeks.

B. Effectiveness Conclusions

The double-blind, saline-controlled study demonstrated that a single injection of 6 mL of Synvisc-One is effective in providing symptomatic relief up to 26 weeks in patients with primary knee OA. There was a statistically significant estimated treatment difference (-0.15, p=0.047) between the Synvisc-One treatment group and the saline control for the primary efficacy endpoint of this study, being the change from baseline over the course of the 26-week study using the patient's assessment of his/her pain (WOMAC LK 3.1 A) (Walking Pain) subscores for patients in the ITT Population.

This study has a favorable risk/benefit profile of a single injection of 6 mL of Synvisc-One in patients with symptomatic primary OA of the knee.

C. Overall Conclusions

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

XII. CDRH DECISION

CDRH issued an approval order on February 26, 2009.

The applicant's manufacturing facility was not needed to be inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIII. 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 are not required: See approval order.

XIV. REFERENCES

1. Altman R, Asch E, Bloch D, et al., Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Arthritis Rheum 1986;29: 1039-1049.

2. Kellgren JH, Lawrence, Radiological assessment of Rheumatoid arthritis. Ann Rheum Dis. 1957; 16(4):485-93

3. Bellamy N, Watson Buchanan W, Goldsmith CH, et al., Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15: 1833-1840.