

FDA Summary for Synvisc-One

Orthopaedic and Rehabilitation Devices Panel

December 9, 2008

FDA Executive Summary

Introduction

This is FDA's Executive Summary for Premarket Approval (PMA) application supplement (P940015/S12), Genzyme Biosurgery's Synvisc-One, a single intra-articular (IA) injection supplied in a 10-mL glass syringe containing 6 mL hylan G-F 20 for treatment of osteoarthritis (OA) in the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g., acetaminophen. Three 2mL articular injections of Synvisc® (hylan G-F 20) were approved in the US (P940015) on August 8, 1997 for the treatment of osteoarthritis (OA) in the knee. The applicant is seeking marketing approval for a modified version (i.e., change in dosing regimen) of that device within the current PMA Supplement (PMA/S).

This PMA/S has been reviewed by the Orthopedic Joint Devices Branch of the Division of General, Restorative, and Neurological Devices with consultation to the Office of Surveillance and Biometrics at the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in the review of this application is greatly appreciated.

The Executive Summary provides an overview of the information provided by Genzyme Biosurgery in P940015/S12. The summary contains a rationale for bringing the device to Panel, an identification of the applicant/manufacture, proposed indications for use, summary of the device description, non-clinical testing, and the clinical study information.

Rationale for Presentation of Synvisc-One to the Panel

This brief section describes the rationale for presentation of this PMA/S to the Orthopaedic and Rehabilitation Devices Advisory Panel. The applicant is seeking marketing approval for Synvisc-One, a single intra-articular (IA) injection supplied in a 10-mL glass syringe containing 6 mL hylan G-F 20 for the treatment of osteoarthritis (OA) in the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g., acetaminophen. Currently, there are no single IA injection hyaluronic acid (HA) viscosupplementation devices approved for use in patients with OA in the knee in the US.

The study conducted by Genzyme and provided within this PMA/S as clinical data intended for the purposes of supporting safety and effectiveness was conducted at 21 sites in 6 European countries. Since no study sites were in the United States, the study was not conducted under an Investigational Device Exemption (IDE). Consequently, the protocol was not prospectively reviewed by FDA. The protocol and WOMAC questionnaire (primary efficacy endpoint tool used in the study) have been included in Sections 8.0 and 9.0 for completeness of the Panel Pack information.

FDA requests your input on the safety and efficacy of Synvisc-One because it is an alternate treatment regimen for a device designed to be injected in the intra-articular space of an osteoarthritic knee for the purpose of reducing knee pain. The Panel members will be asked to evaluate and discuss the presented data for the proposed indication and intended use, and provide input regarding the interpretation of the results from the clinical study.

FDA is presenting Synvisc-One to the Panel primarily to comment on the clinical effectiveness of the device in relieving pain in patients who have osteoarthritis of the knee.

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Applicant/Manufacturer Information

Applicant/Manufacturer Name and Address:

GENZYME Corporation
55 Cambridge Parkway, 4th Floor
Cambridge MA 02142
USA

Indications for Use

The applicant has proposed the following 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.

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.

Device Description

Synvisc-One™ (hylan G-F 20) is supplied in a 10-mL glass syringe containing 6 mL of hylan G-F 20 and is administered as a single intra-articular (IA) injection.

Synvisc has been approved for a total of three injections (2mL of Synvisc per each injection supplied in a 2.25mL glass syringe) for the treatment of osteoarthritis (OA) in the knee for patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics on August 8, 1997 in the US (P940015).

The material of Synvisc and Synvisc-One is the identical hylan G-F 20 and the manufacturing process for hylan G-F 20 material remains unchanged.

Hylan G-F 20 is a sterile, non-pyrogenic, fluid containing hylan polymers (produced from chicken combs) hydrated in physiological saline. Hylans are cross-linked derivatives of hyaluronan (sodium hyaluronate), a natural complex sugar of the glycosaminoglycan family. Hylan G-F 20 consists of two different hylans. Hylan A is a water soluble hyaluronan derivative (hylan A fluid). Hylan B is a water insoluble hylan derivative, which forms a hydrated gel in aqueous solvents (hylan B gel). After homogenization, it forms a gel slurry. Hylan A fluid constitutes 80% (per volume) and hylan B gel slurry 20% (per volume) of the final hylan G-F 20 device.

Hylan A is extracted from chicken combs after treatment of the comb tissue with a solution containing formaldehyde. The formaldehyde introduces a limited number of crosslinks between polysaccharide chains to yield a soluble molecule with increased molecular weight (4 to 8 million g/mol). Hylan B is produced by chemically cross-linking hylan molecules with vinyl sulfone to form an infinite molecular network. It is a water-insoluble, viscoelastic hydrated gel.

Synvisc-One is supplied in a 10-mL glass syringe containing the equivalent volume of 3 doses (total of 6 mL) of hylan G-F 20 used in Synvisc. The contents of the syringe are sterile and non-pyrogenic. One milliliter of hylan G-F 20 contains 8 mg of hylan polymer. The hydration fluid is isotonic physiological sodium chloride solution. Table 1 identifies the specific contents of each 10mL syringe of Synvisc-One.

Table 1: Contents of each 10-mL syringe of Synvisc-One

Contents	Per 10mL Syringe
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 (USP)	q.s. to 6.0 mL

Non-Clinical Testing

The material of Synvisc (P940015) and Synvisc-One is the identical hylan G-F 20 which is either supplied in a 2.25-mL glass syringe or a 10-mL glass syringe (Synvisc-One). The manufacturing process for hylan G-F 20 material remains unchanged.

Biocompatibility:

The biocompatibility testing requirements for this device include:

- Cytotoxicity
- Sensitization
- Genotoxicity
- Implantation

All of these tests were previously conducted on the final product approved in P940015 and were found to meet the requirements of the tests.

Non-Clinical Safety Testing of Delivery Components:

Genzyme Corporation and/or its suppliers received approval from FDA in August, 1997 for Synvisc, and had performed safety testing on the delivery components, in compliance with the US and European guidelines. Testing described in this section was performed to ensure that the Synvisc-One 10-mL syringe product contacting materials are biocompatible.

Specifically, Genzyme conducted GLP cytotoxicity and sensitization (guinea pig maximization test) studies to further ensure safety of the stopper on the original Synvisc device. These studies were acceptable to support the proposed device modifications:

- Cytotoxicity Study Using ISO Elution Method (Genzyme study 04008)
- ISO Maximization Sensitization Study – Extract (Genzyme study 04007)

Clearance:

The applicant also conducted clearance tests to determine the longevity of hylan G-F 20. A tritium radiolabel was incorporated into the polysaccharide chain of hylan gel in order to quantitatively follow the material after injection into rabbit knee joints. Animals were sacrificed at 1, 10, 20 and 30 days after the injection to determine the quantity of radioactivity which could be recovered, and its distribution among individual joint tissues and in the major internal organs. The clearance of tritiated gel from the joint was found to follow a first order decay function with a half life of 7.7 ± 1 days. We recognize that the dosing regimen is different for Synvisc-One in comparison to Synvisc, but we are not concerned about the toxicity aspects of Synvisc-One based upon the ability of Synvisc to clear the body.

Summary:

The applicant provided the results of the overall safety testings conducted on Synvisc (hylan), the syringe barrel and stopper, the device and device-contacting components. The materials used to manufacture the Synvisc-One 10.0-mL syringe are equivalent to the components used in the manufacture of the currently marketed Synvisc product, and is considered to be safe.

Clinical Study Overview

Overall Study Description:

The applicant has presented data from a pivotal study conducted outside the US (OUS). The study was a randomized, multi-center, parallel, double-blind, blinded evaluator, placebo-controlled 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 (Synvisc-One: n=124, Placebo: n=129) between May 2005 to September 2006 as part of this pivotal study.

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.

It should be noted that this study was not conducted in the US and nor was the study conducted under an Investigational Device Exemption (IDE). Consequently, the Agency did not review the protocol prior to the conduct of the study.

Overall Study Objectives:

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 Placebo [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.

Study Design:

The Initial Treatment Phase Study

Patients were required to have a documented diagnosis of OA of the target knee made at least 3 months prior to Screening. Patients with bilateral OA of the knees could be enrolled and have 1 knee treated according to the study protocol, as long as the contralateral (non-target) knee could be managed by paracetamol alone. Bilateral OA patients with symptomatic OA of the contralateral knee or either hip that was not responsive to paracetamol and required other therapy were excluded from this study. Two hundred fifty-three (253) patients were randomized (Synvisc: n=124, Placebo: n=129) in this OUS study.

- **Key Inclusion Criteria:**

All patients met the American College of Rheumatology (ACR) criteria for OA (Altman, 1986, *Arthritis Rheum*). 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 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC LK 3.1) A1 (pain while walking on flat surface); and
- A mean score of 1.5 to 3.5 on all five questions of the WOMAC LK 3.1 A (pain).

- Key Exclusion Criteria:

The main initial phase exclusion criteria were the following:

- Grade IV radiographic stage of the target knee according to the system of Kellgren and Lawrence (K-L) (Kellgren, 1957, *Ann Rheum Dis*);
- 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.

- 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 for details on the windows for the study treatments).

- 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 anteroposterior (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.

- 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.

- 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 [Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC LK 3.1) which includes Pain score A, and subscore A1, Patient Global Assessment (PTGA)], and the Blinded Evaluator completed the Clinician Observer Global Assessment (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.

- Co-Treatments and/or Co-Medications:

The protocol included specifics regarding the allowable and prohibited medications throughout the duration of the study. Tables 2 and 3 include a listing of permitted and/or prohibited co-treatments and/or co-medications throughout the study.

Table 2. 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 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 exceed recommended dosing in product information. Not taken for more than 5 consecutive days 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 3. 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)
- 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 ≤ 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 4. 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) which includes 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 4. Schedule of Study Events

	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	-21 days ⁸ to	Day 0	Week 1 (+ 4 days)	Week 4 (+ 4 days)	Week 8 (+ 7 days)	Week 12 (+ 7 days)	Week 18 (+ 7 days)	Week 26 (+ 7 days)
Informed Consent	X ⁴							
Study Eligibility	X	X						X ¹⁰
Demographics and Height and Weight	X							
Vital sign		X						X
Medical History	X							
Physical Examination								X
Target Knee Assessment	X	X	X	X	X	X	X	X
Pregnancy Test ¹		X ¹						X
Radiograph ²	X ²							
Prior Treatment and Medications ³	X ³							
Prohibited Medication Washout ⁴	X ⁴							
Rescue Medication Monitoring		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 Recording	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 prohibited medications. All Baseline evaluations occurred prior to CTM administration.
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

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 above for the Initial Treatment Phase) continued to apply throughout the Repeat Treatment Phase.

- **Inclusion Criteria:**

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:

1. Must have continued to meet Screening Inclusion/Exclusion criteria
2. Must have had no major safety concerns during the first course of treatment as assessed by the Investigator
3. Must have had a WOMAC LK 3.1 A (Pain) score of at least 1
4. Must, in the Investigator's clinical assessment, have been a candidate for treatment
5. 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.

- **Follow-up Schedule:**

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.

Prospective Endpoints of the Initial Treatment Phase Study:

As previously noted, since this study was not conducted under an Investigational Device Exemption (IDE), the Agency did not review the protocol, the prospectively-defined endpoints, or proposed analyses prior to the conduct of the study.

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 Objective:**

To demonstrate that 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 Placebo (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 to the 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).
- Tertiary Efficacy Objectives:
 - To analyze the differences between the Total WOMAC score 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 B 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 average daily consumption of paracetamol (grams) over 26 weeks in the Synvisc-one treatment group and the Placebo group.

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 Placebo group at the 5% significance level. Statistical inference was based on a repeated measures of Analysis of Covariance (ANCOVA). The criteria for success for the study was not reviewed or approved by the Agency since the study was not conducted under a US IDE.

Sample Size 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 following assumptions were made to compute the sample size:

- The 2-sample t-test comparing the within-treatment group means of the patient specific mean change from Baseline is used. The 2-sample t-test approximates the test of the null hypothesis based on the repeated measures model that was used in the primary efficacy analysis.
- Overall treatment difference of 0.297
- Common standard deviation (SD) of 0.725
- Dropout rate of 25%
- Two-sided significance level of 5%

With these assumptions, a sample size of approximately 250 (125 patients per treatment arm) would provide over 80% power to detect an overall difference of 0.297 (WOMAC LK 3.1 A) between the Synvisc-One treatment group and the Placebo group over the course of 26 weeks.

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.

Statistical Methods

Pain relief as measured at Baseline and follow-up study visits with the WOMAC LK 3.1 A subscale provided the basis for the primary efficacy objective:

- To demonstrate that 1 x 6-mL injection of Synvisc-One provides superior pain relief (WOMAC LK 3.1 A) over 26 weeks as compared to a 1 x 6-mL IA injection of Placebo in treating patients with symptomatic primary OA of the knee.

The primary efficacy objective was tested using the null hypothesis that there is no difference in the mean change from Baseline measure of pain relief (WOMAC LK 3.1 A) between Synvisc-One and Placebo over 26 weeks. This can be expressed as the hypothesis test,

$$H_0 : \delta_{over} = 0 \text{ vs. } H_A : \delta_{over} \neq 0$$

where δ_{over} is the mean difference in the change from Baseline measure of pain relief (WOMAC LK 3.1 A) between the Synvisc-One treatment group and the Placebo group over all of the post-Baseline study visits (Weeks 4, 8, 12, 18, 26).

The WOMAC LK 3.1 A value used in all analyses was calculated by taking the mean value of the 5 scores which comprise the WOMAC A subscale.

- Effectiveness Analyses:

The primary efficacy analysis was to be 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). The description of the repeated measures model that was fit to the data and the construction of the test statistic that was used for the primary efficacy objective follows:

Model: The WOMAC LK 3.1 A subscore outcome vector for each patient consisted of the change from baseline to each post-Baseline measurement. The outcome vector was modeled with a repeated measure analysis of Covariance (ANCOVA) model that included terms for treatment, site, time and time-by-treatment interaction, as well as the Baseline WOMAC LK 3.1 A subscore as a covariate. For the analysis of the percentages of positive responders, patients who discontinued the study prior to the Week 26 assessment due to either target knee-related AEs or due to lack of efficacy were classified as non-responders in the efficacy analysis. Patients who discontinued the study for other reasons had their responder status imputed using the Last Observation Carried Forward (LOCF) method. The LOCF was used for all responder analyses, but not for the analysis of other parameters.

No interim analysis was performed for this study.

- Safety Analyses:

The safety analyses were to be 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.

Accounting:

A total of 253 patients were randomized to either receive Synvisc-One (124) or to receive Placebo (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.

Patient Demographics

Baseline patient demographics for the Initial Treatment Phase of the study are outlined in Table 5 and for the Repeat Treatment Phase to assess safety are outlined in Table 6.

Table 5. Summary of Demographic and Baseline Characteristics - ITT Population

	Synvisc –One (N=124)	Placebo (N=129)	Total (N=253)
Parameter/Category			
Age			
N	124	129	253
Mean (SD)	63.6 (9.64)	62.5 (9.17)	63.0 (9.40)
Median	64.0	63.0	63.0
Range	42 to 83	43 to 84	42 to 84
Sex, n			
Male, n (%)	32 (25.8)	41 (31.8)	73 (28.9)
Female, n (%)	92 (74.2)	88 (68.2)	180 (71.1)
Race, n			
Caucasian, n (%)	118 (95.2)	125 (96.9)	243 (96.0)
Black, n (%)	5 (4.0)	3(2.3)	8 (3.2)
Hispanic, n (%)	0	0	0
Asian, n (%)	0	1 (0.8)	1 (0.4)
Other, n (%)	1 (0.8)	0	1 (0.4)
Weight (kg)			
n	123	129	252
Mean (SD)	79.38 (14.049)	82.35 (16.120)	80.90 (15.188)
Median	78.60	80.00	79.00
Range	49.0, 132.9	53.0, 126.0	49.0, 132.9
Height (cm)			
N	123	129	252
Mean (SD)	165.3 (9.21)	166.4 (8.74)	165.9 (8.97)
Median	165.0	165.0	165.0
Range	145, 188	148, 191	145, 191
Body Mass Index (kg/m2)			
n	123	129	252
Mean (SD)	29.08 (4.814)	29.77 (5.742)	29.43 (5.310)
Median	28.41	28.65	28.63
Range	20.7, 46.0	19.5, 52.4	19.5, 52.4

Table 6. Summary of Demographic and Baseline Characteristics – Repeat Treatment Safety Population

	Synvisc-One-Synvisc-One* (N=77)	Placebo-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.

Patient Accounting

Table 7 identifies patient dispositions at 6 months of the Intent-to-Treat (ITT) and per protocol populations (PPP) for the Initial Treatment Phase Study. Table 8 identifies patient dispositions at 4 weeks for the Repeat Treatment Phase of the study.

Table 7. 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 8. 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.

Clinical Results

The clinical data the applicant collected to demonstrate the safety and effectiveness of Synvisc-One is presented in this Section.

Safety Results:

Adverse Events (AEs) in the Initial Treatment Phase of the Study

Adverse Events (AEs) in the Initial Treatment Phase of the Study were collected and recorded from the time the patient signed the informed consent until study completion. The AEs for the patients enrolled in the Initial Treatment Phase of the Study are presented in Tables 9 through 13 below.

Overall, during the Initial Treatment Phase of the study, 70 (56.9%) patients in the Synvisc-One group and 79 (60.8%) patients in the Placebo (PBS) group experienced at least one AE. Of these, 4 patients (3.3%) in the Synvisc-One group and 2 patients (1.5%) in the Placebo group had AEs that were assessed by the Investigator to be related to study treatment and 7 patients (5.7%) in the Synvisc-One group and 5 patients (3.8%) in the Placebo group had AEs there were assessed by the Investigator to be related to the study procedure. These specific results are presented in Table 9.

Table 9. Summary of Treatment-Emergent Adverse Events During the Initial Treatment Phase - Safety Population

Patients	Synvisc-One (N = 123)		Placebo (N = 130)		Overall (N = 253)	
	n (%)	No. of Events	n (%)	No. of Events	n (%)	No. of Events
With an AE	70 (56.9)	177	79 (60.8)	224	149 (58.9)	401
With an Injection Procedure-Related AE	7 (5.7)	7	5 (3.8)	5	12 (4.7)	12
With a Treatment-Related AE	4 (3.3)	5	2 (1.5)	2	6 (2.4)	7
Who Prematurely Discontinued Because of an AE	1 (0.8)	1	3 (2.3)	7	4 (1.6)	8
With a Target Knee AE	44 (35.8)	77	44 (33.8)	82	88 (34.8)	159
With an Injection Procedure-Related Target Knee AE	6 (4.9)	6	4 (3.1)	4	10 (4.0)	10
With a Treatment-Related Target Knee AE	4 (3.3)	5	1 (0.8)	1	5 (2.0)	6
With an Injection Procedure-Related Target Knee AE and/or a Treatment-Related Target Knee AE	7 (5.7)	--	4 (3.1)	--	11 (4.3)	--
With a Target Knee Serious AE	0	0	0	0	0	0
Whose Highest Severity of AE is:						
Mild	26 (21.1)	40	35 (26.9)	81	61 (24.1)	121
Moderate	36 (29.3)	64	39 (30.0)	75	75 (29.6)	139
Severe	8 (6.5)	11	5 (3.8)	6	13 (5.1)	17

Note: Patients may be counted in more than 1 category.

Note: Treatment groups reflect the actual treatment received, not the randomized treatment.

As summarized in Table 10, AEs in the target knee for patients in the Initial Treatment Phase of the Study occurred in 44 (35.8%) patients in the Synvisc-One group and 44 (33.8%) patients in the Placebo group. The most commonly occurring target knee AEs were arthralgia (Synvisc-One: n=31, 25.2%; Placebo: n=28, 21.5%), joint stiffness (Synvisc-One: n=10, 8.1%; Placebo: n=13, 10.0%), and joint effusion (Synvisc-One: n=7, 5.7%; Placebo: n=7, 5.4%).

Table 10. Adverse Events in the Target Knee Occurring in >1 Patient in Either Group- Safety Population

Preferred Term	Synvisc-One N =123 n (%)	Placebo N =130 n (%)	Total N = 253 n (%)
Any Treatment-Emergent Adverse Event	44 (35.8)	44 (33.8)	88 (34.8)
Arthralgia	31 (25.2)	28 (21.5)	59 (23.3)
Joint stiffness	10 (8.1)	13 (10.0)	23 (9.1)
Joint effusion	7 (5.7)	7 (5.4)	14 (5.5)
Joint swelling	5 (4.1)	7 (5.4)	12 (4.7)
Joint warmth	2 (1.6)	5 (3.8)	7 (2.8)
Post-traumatic pain	0	3 (2.3)	3 (1.2)
Synovial cyst	0	2 (1.5)	2 (0.8)

Note: Patients are counted once for each unique AE and may have had more than one unique AE. The AEs are ordered in decreasing frequency based on their number in the Synvisc-One treatment group. AEs are coded using MedDRA terminology.

Note: Treatment groups reflect the actual treatment received, not the randomized treatment.

Study treatment-related target knee AEs are summarized in Tables 11 and 12. Overall, 5 patients (2.0%) had treatment-related target knee AEs (Synvisc-One: n=4, 3.3%; Placebo: 1, 0.8%). The most frequently reported study treatment-related target knee AEs was arthralgia (Synvisc-One: n=1, 0.8%; Placebo: n=1, 0.8%). Of these treatment-related target knee AEs, all were of mild or moderate severity.

Table 11. Target Knee Adverse Events Related to Treatment - Safety Population

Preferred Term	Synvisc-One N =123 n (%)	Placebo N =130 n (%)	Total N = 253 n (%)
Any AEs	4 (3.3)	1 (0.8)	5 (2.0)
Arthralgia	1 (0.8)	1 (0.8)	2 (0.8)
Arthritis	1 (0.8)	0	1 (0.4)
Joint effusion	1(0.8)	0	1 (0.4)
Injection site pain	1(0.8)	0	1 (0.4)

Note: Related to Treatment = Unknown Relationship to Treatment or Possibly, Probably, or Definitely Related to Treatment. Patients are counted once for each unique AE and may have had more than one unique AE. The AEs are ordered by decreasing frequency based on their number in the Synvisc-One treatment group. AEs are coded using MedDRA terminology.

Note: If a patient had more than one occurrence of the same AE, the strongest relationship to study treatment was included.

Table 12. Patients with Study Treatment-Related Target Knee AEs - Safety Population

Patient I.D.	AE Preferred Term	AE Verbatim Term	Relationship to Study Treatment	Severity
Synvisc-One				
07007	Injection site pain	Pain during injection at target knee	Probable	Mild
08004	Arthritis	Arthritis of the target knee	Probable	Moderate
13002	Joint effusion	Knee effusion	Possible	Mild
19013	Arthralgia	Pain in target knee after injection	Probable	Moderate
19013	Arthralgia	Pain in target knee	Possible	Mild
Placebo				
19020	Arthralgia	Pain in target knee after injection radiating to lower leg	Possible	Moderate

Procedure-related target knee AEs are summarized in Table 13. Six patients (4.9%) in the Synvisc-One group and 4 patients (3.1%) in the Placebo group had target knee AEs that were assessed by the Investigator to be related to the study procedure. The most frequently reported target knee AEs considered related to the procedure include arthralgia (Synvisc-One: n=2, 1.6%; Placebo: n=3, 2.3%) and joint effusion (Synvisc-One: n=2, 1.6%; Placebo: n=0). Of these procedure-related, target knee AEs, all were of mild or moderate severity.

Table 13. Target Knee Adverse Events Related to Procedure- Safety Population

Preferred Term	Synvisc-One N = 123 n (%)	Placebo N = 130 n (%)	Total N = 253 n (%)
Any AEs	6 (4.9)	4 (3.1)	10 (4.0)
Arthralgia	2 (1.6)	3 (2.3)	5 (2.0)
Joint effusion	2 (1.6)	0	2 (0.8)
Arthritis	1 (0.8)	0	1 (0.4)
Arthropathy	1 (0.8)	0	1 (0.4)
Injection site pain	0	1 (0.8)	1 (0.4)

Note: Patients are counted once for each unique AE and may have had more than 1 unique AE. The AEs under each class are ordered in decreasing frequency based on their total count. AEs are coded using MedDRA terminology.

Note: If a patient had more than 1 occurrence of the same AE, the strongest relationship to injection procedure was included.

Note: Treatment groups reflect the actual treatment received, not the randomized treatment.

Adverse Events in the Repeat Treatment Phase of the Study

During the 4-week Repeat Treatment Phase of the study, 9 (11.7%) patients in the Synvisc One – Synvisc One group and 13 (15.7%) patients in the Placebo-Synvisc One group experienced at least one AE. Four patients (5.2%) in the Synvisc One- Synvisc One group and 7 patients (8.4%) in the Placebo-Synvisc One group had an injection procedure-related and/or a treatment-related target knee AE. One patient (1.3%) in the Synvisc One-Synvisc One group and 6 patients (7.2%) in the Placebo-Synvisc One group had AEs that were assessed by the Investigator to be related to study treatment and 4 patients (5.2%) in the Synvisc One-Synvisc One group and 7 patients (8.4%) in the Placebo-Synvisc One group had AEs that were assessed by the Investigator to be related to the study procedure. One patient (1.3%) in the Synvisc One-Synvisc One group and 6 patients (7.2%) in the Placebo-Synvisc One group had target knee AEs that were assessed by the Investigator to be related to the study treatment. These adverse events are summarized in Table 14.

Table 14. Summary of Treatment-Emergent Adverse Events – Synvisc One-Synvisc One Patients in the Repeat Treatment Phase Only

	Synvisc One - Synvisc One (n=77) n (%)	Placebo-Synvisc One (n=83) n (%)
With an AE	9 (11.7)	13 (15.7)
With a Procedure- Related AE	4 (5.2)	7 (8.4)
With a Treatment-Related AE	1 (1.3)	6 (7.2)
With an Injection Procedure-Related “Other” AE and/or a Treatment- Related AE	0	0
With a Serious AE	0	2 (2.4)
Who Died	0	1 (1.2)
With a Target Knee AE	4 (5.2)	7 (8.4)
With an Injection Procedure-Related Target Knee AE and/or a Treatment- Related Target Knee AE	4 (5.2)	7 (8.4)
With a Procedure- Related Target Knee AE	4 (5.2)	7 (8.4)
With a Treatment-Related Target Knee AE	1 (1.3)	6 (7.2)
With a Serious AE in the Target Knee	0	0

Note: Patients may be counted in more than one category.

Note: Treatment groups reflect the actual treatment received, not the randomized treatment.

Note: Treatment group reflects prior treatment. Patient 08009 received Placebo during Repeat Treatment and is not summarized.

Note: Patients are counted once for each unique AE and may have had more than one unique AE. AEs are coded using MedDRA terminology.

Note: If a patient had more than one occurrence of the same AE, the strongest relationship to injection procedure was included.

Four patients (5.2%) in the Synvisc One - Synvisc One group and 7 patients (8.4%) in the Placebo - Synvisc One group had target knee AEs that were assessed by the Investigator to be related to the study procedure during the Repeat Treatment Phase of the study. The most commonly occurring target knee AEs during the Repeat Treatment Phase were arthralgia (Synvisc One: n=3, 3.9%; Placebo: n=1, 1.2%), injection site pain (Synvisc One: n=1, 1.3%; Placebo: n=2, 2.4%), and synovial cyst (Synvisc One: n=0; Placebo: n=2, 2.4%). One patient (1.3%) in the Synvisc One - Synvisc One group and 6 patients (7.2%) in the Placebo - Synvisc One group had target knee AEs that were assessed by the Investigator to be related

to study treatment. All AEs were of mild or moderate severity. These adverse events are summarized in Tables 15 and 16.

Table 15. Patients with Treatment-Related Target Knee AEs During the Repeat Treatment Phase of the Study – Repeat Safety Population

Patient I.D.	AE Verbatim Term	AE Preferred Term	Relationship to Study Treatment	Severity
Synvisc One - Synvisc One				
07011	Target knee pain	Arthralgia	Probable	Mild
Placebo - Synvisc One				
03008	Bakers cyst	Synovial cyst	Possible	Moderate
10001	Injection pain in target knee	Injection site pain	Definite	Mild
10005	Target knee pain	Arthralgia	Probable	Moderate
14009	Swelling of popliteal cyst	Synovial cyst	Possible	Mild
14009	Numbness left lower limb and foot	Hypoesthesia	Possible	Mild
17905	Irritated knee after injection	Arthropathy	Probable	Mild
19014	Pain left knee(injection site)	Injection site pain	Possible	Mild

Table 16. Patients with Study Procedure -Related Target Knee AEs during the Repeat Treatment Phase of the Study – Repeat Safety Population

Patient I.D.	AE Verbatim Term	AE Preferred Term	Severity
Synvisc One-Synvisc One			
07011	Target knee pain	Arthralgia	Mild
09034	Flare of OA target knee	Arthritis	Mild
11001	Small hematoma after injection, target knee, injection site	Injection site haematoma	Mild
19007	Pain at injection site	Injection site pain	Mild
19007	Pain in target knee after injection	Arthralgia	Mild
Placebo - Synvisc One			
03008	Bakers cyst	Synovial cyst	Moderate
10001	Injection pain in target knee	Injection site pain	Mild
10005	Target knee pain	Arthralgia	Moderate
11022	Knee swelling	Joint swelling	Mild
14009	Swelling of popliteal cyst	Synovial cyst	Mild
14009	Numbness left lower limb and foot	Hypoaesthesia	Mild
17905	Irritated knee after injection	Arthropathy	Mild
19014	Pain left knee (injection site)	Injection site pain	Mild

No patients in the Repeat Safety Population experienced target knee severe AEs related to the device ($p=0.061$ in two-sided Fisher’s Exact test). The exact 95% Confidence Interval of the AE rate of 2.8% (5/177) is (0.92%, 6.47%), assuming a binomial distribution, counting the patient who have more than one adverse event as one event.

Summary of All Adverse Events Occurring in > 1 Patient in Either Group

Overall, 101 patients (Synvisc One: $n=47$, 38.2%; Placebo: $n=54$, 41.5%) experienced at least one “Other” AE. The most commonly occurring “Other” AEs are presented in Table 17. In the both groups, headache (Synvisc One: $n=9$, 7.3%; Placebo: $n=15$, 11.5%), back pain (Synvisc One: $n=8$, 6.5%; Placebo: $n=10$, 7.7%), and nasopharyngitis (Synvisc One: $n=5$, 4.1%; Placebo: $n=7$, 5.4%) were the most common. In the Placebo group, 7 patients (5.4%) also experienced influenza.

Table 17. Other Adverse Events Occurring in > 1 Patient in Either Group – Safety Population

Preferred Term	Synvisc-One N =123 n (%)	Placebo N = 130 n (%)	Total N = 253 n (%)
Any Treatment-Emergent AE	47 (38.2)	54 (41.5)	101 (39.9)
Headache	9 (7.3)	15 (11.5)	24 (9.5)
Back pain	8 (6.5)	10 (7.7)	18 (7.1)
Nasopharyngitis	5 (4.1)	7 (5.4)	12 (4.7)
Influenza	4 (3.3)	7 (5.4)	11 (4.3)
Arthralgia	3 (2.4)	3 (2.3)	6 (2.4)
Post-traumatic pain	3 (2.4)	3 (2.3)	6 (2.4)
Shoulder pain	4 (3.3)	2 (1.5)	6 (2.4)
Bronchitis	2 (1.6)	3 (2.3)	5 (2.0)
Neck pain	1 (0.8)	3 (2.3)	4 (1.6)
Pain in extremity	1 (0.8)	3 (2.3)	4 (1.6)
Pharyngitis	3 (2.4)	1 (0.8)	4 (1.6)
Respiratory tract infection	3 (2.4)	1(0.8)	4 (1.6)
Sciatica	2 (1.6)	1 (0.8)	3 (1.2)
Cystitis	2 (1.6)	0	2 (0.8)
Hypertension	2 (1.6)	0	2 (0.8)
Nausea	0	2 (1.5)	2 (0.8)
Oedema peripheral	0	2 (1.5)	2 (0.8)
Osteoarthritis	0	2 (1.5)	2 (0.8)
Sinusitis	2 (1.6)	0	2 (0.8)

1 'Other' adverse events occurred at locations other than the target knee.

Note: Patients are counted once for each unique AE and may have had more than one unique AE. The adverse events are ordered in a decreasing frequency based on their total count. AEs are coded using MedDRA terminology. Note: Treatment groups reflect the actual treatment received, not the randomized treatment.

“Other” AEs that were considered by the Investigator to be possibly, probably, or definitely related to the injection procedure are summarized by the MedDRA System Organ Class and Preferred Term.

Treatment-emergent “Other” AEs that the Investigator considered related to the injection procedure include nausea (Synvisc-One: n=0; Placebo: n=1, 0.8%), and vasovagal syncope (Synvisc-One: n=1, 0.8%; Placebo: n=0).

Effectiveness Results:

Primary Endpoint Analysis Provided by the Applicant

As pre-specified in the applicant’s Statistical Analysis Plan (SAP), the applicant analyzed the WOMAC A pain scores from baseline through 26 weeks using a longitudinal data analysis, showing that there was a statistically significant difference with a p-value of 0.047 and its difference of the treatment effect being 0.15 in favor of Synvisc-One at 26 weeks. These results were based on repeated measures ANCOVA using a fixed model, including terms for treatment, site, time and time by-treatment interaction, as well as the baseline WOMAC Subscale A score as a covariate. The scale used in this WOMAC L.K.3.1 is the 5 Likert scales: 0=none, 1 =mild, 2=moderate, 3=severe and 4=extreme. The change in the WOMAC LK

3.1 A pain subscore is presented in Table 18.

Table 18. WOMAC LK 3.1 A Pain Subscore Overall Change From Baseline – ITT Population using a fixed model of ANCOVA

	Baseline Mean(SE)	Overall Mean(SE)	Estimated Change (SE)	Estimated least square mean difference between Synvisc-One and Placebo (SE)	2-sided 95% CI for the difference (δ) of two mean changes from baseline	p-value
Synvisc-One (n=124)	2.30 (0.038)	1.43 (0.060)	-0.84 (0.060)	-0.15 (0.076)	-0.30 < δ < -0.002	0.047
Placebo (n=129)	2.25 (0.036)	1.59 (0.058)	-0.69 (0.058)			

WOMAC LK 3.1 A Pain Sub score including pain 1) when walking on flat surface, 2) when going up and down, 3) at night while in bed, 4) while in sitting or lying down, and 5) when standing

FDA acknowledges that based upon the applicant’s pre-specified analyses provided in the PMA/S, there was a statistically significant difference in pain reduction between the two groups at the 0.05 significance level, albeit small. However, it should also be noted that the sample size assumptions for the study to provide 80% power were based on detecting an overall difference of 0.297 (WOMAC LK 3.1 A). Consequently, it should be noted that the observed difference was less than predicted; hence the study appears to have been underpowered to appropriately detect the small differences between the two groups given the small sample size.

FDA indicated that the difference of 0.15 Likert scale between the Synvisc-One and the Placebo control at 26 weeks can be assumed to be equivalent to a difference of 3mm in the least squares mean, if converted into the 100mm Visual Analog Pain scale (VAS). FDA also indicated to the applicant that a difference of at least 10mm of pain reduction between Synvisc-One and the Placebo groups on the whole 100 VAS seemed to be a reasonable expectation for demonstrating a clinically-meaningful difference. Consequently, given the difference obtained from the study conducted by the applicant to support the safety and effectiveness of this device, it is uncertain as to whether the observed difference translates into a clinically-meaningful difference between the two groups.

FDA will be asking the Panel a question related to this issue.

Analyses Requested by FDA for the Primary Endpoint

Since the study was conducted at 21 sites in six OUS countries, FDA requested, as part of the review of the application, that the random effects of site be included in the analyses of the primary endpoint. Specifically, FDA requested that the applicant reanalyze the primary endpoint, using a mixed model of analysis of covariance (ANCOVA), with fixed and random effects included within the mixed model of the analysis of covariance. Genzyme provided the requested re-analysis, using a mixed model of ANCOVA, as part of follow-up emails and teleconferences with the Agency.

The result of the applicant’s analysis of the WOMAC A pain scores from baseline through 26 weeks using a mixed model for a longitudinal data analysis demonstrated that there was a statistically significant difference with a p-value of 0.0322 with the difference of the treatment effect being 0.1543. Based on the analysis, the 95% lower and upper confidence interval of the difference in the least square mean of the

WOMAC subscale A was $-0.2956 < \delta < -0.01312$ in favor of Synvisc-One. Results were based on repeated measures of a mixed model of ANCOVA including terms for treatment, site, time and time by-treatment interaction, as well as the baseline WOMAC Subscale A score as a covariate. The Agency reaffirmed the analyses and obtained differences in the LS mean between the two groups in the results from those presented by the applicant (see Table 19).

Table 19. WOMAC LK 3.1 A Pain Subscore Overall for Least Square Mean Difference – ITT Population, using a mixed model (FDA requested analysis)

	Baseline Mean(SE)	LS Mean*(SE)	Estimated least square mean difference between Synvisc-One and Placebo (SE)	2-sided 95% CI for the difference of two mean changes from baseline	p-value
Synvisc-One (n=124)	2.30 (0.038)	1.3967 (0.0728)	-0.1543 (0.07198)	-0.2956 < δ < -0.0131	0.0322
Placebo (n=129)	2.25 (0.036)	1.5511 (0.0715)			

WOMAC LK 3.1 A Pain Sub score including pain 1) when walking at flat surface, 2) when going up and down, 3) at night while in bed, 4) while in sitting or lying down, and 5) when standing

* LS mean:Least square mean

Note. The above table is from the reanalysis of the primary endpoint using a mixed model of ANCOVA requested by FDA after receipt of the applicant’s response (dated June 25, 2008) provided in Amendment 4 to FDA’s deficiency letter was submitted. The above result is from the model which the FDA believes is most appropriate.

As previously noted, the Agency could not define nor prospectively address how much pain reduction should exist for the study to be considered a success since the Agency did not review the protocol prior to its initiation outside the US. For regulation of these types of devices, where there may exist a substantial placebo effect, FDA has requested that an appropriately designed study should demonstrate both a statistically significant and a clinically meaningful difference between the groups (Synvisc-One and placebo PBS).

Based upon the results, the study appears to be underpowered to be able to accurately detect a small difference between the two groups with the applicant's sample size calculation, which was based on a detectable difference of 0.297. Since the observed difference between the Synvisc-One and Placebo groups was 0.1543, the sample size was underpowered to detect smaller differences than the original hypothetical value of 0.297. Consequently, a larger sample size would be necessary statistically to appropriately detect such small differences for fixed power and Type-1 error rate.

Please note that p-values are determined by the difference and the size of the standard error regardless of being able to accurately detect a small difference between the two groups. Based upon the results from the applicant’s study, a difference of a decrease of one scale in the pain reduction on WOMAC A between the Synvisc-One and Placebo groups does not exist.

The applicant also has presented information from published literature comparing other pharmacological agents, such as non-steroidal anti-inflammatory drugs, with Synvisc-One in pain reduction as a rationale to support that their product is effective

FDA will be asking the Panel a question related to this issue.

Secondary Endpoints

The original protocol and statistical analysis plan (SAP) have been included in Sections 9.0 and 10.0 within the Panel Pack for completeness.

As pre-specified in the applicant’s SAP, the applicant analyzed the continuous secondary endpoints with a fixed effects model of ANCOVA (Table 20) and categorical endpoints using a proportional odds model (Table 21). Table 20 shows the results of the secondary endpoints, using a fixed model of ANCOVA for the continuous scores of Likert scale of the WOMAC subscores as requested by FDA. The differences in the least square mean between Synvisc-One and Placebo control showed either no statistical significance or marginal differences when a statistical significance existed.

Table 20. Secondary endpoints: WOMAC LK 3.1 A Pain Subscore (Likert scale) week 26 From Baseline – ITT Population, using a fixed effects model of ANCOVA

	Synvisc-One (n=124) baseline	Placebo (n=129) baseline	Synvisc-One (n=124) (SE) change from baseline	Placebo (n=129) (SE) change from baseline	Estimated Difference in Change from baseline (Placebo – Synvisc-One)	2-sided 95% CI for the difference of two mean changes at 26 weeks from baseline	p-value
Applicant’s Pre-Specified Analysis							
WOMAC LK A at 26 weeks	2.25	2.30	76 (0.074)	0.58 (0.073)	-0.18 (0.097)	- 0.372 < δ < 0.0109	0.064
The Applicant’s Re-Analyses (in response to FDA’s October 3, 2007 dated deficiency letter)							
WOMAC LK A1 (pain on walking) overall 26 weeks	2.39	2.33	- 0.88(0.07)	- 0.70(0.06)	-0.18 (0.083)	- 0.346 < δ < 0.019	0.029
PTGA overall over 26 weeks	2.57	2.50	-0.73(0.06)	- 0.60(0.06)	-0.13 (0.08)	- 0.287 < δ < 0.024	0.099
COGA overall over 26 weeks	2.44	2.49	-0.66(0.06)	- 0.53(0.06)	-0.13 (0.08)	- 0.278 < δ < 0.026	0.101
WOMAC C overall 26 weeks	2.29	2.28	-0.66(0.061)	-0.63 (0.059)	-0.03 (0.077)	- 0.18 < δ < 0.12	0.679

WOMAC LK A1: Pain on walking on flat surface, using 5 Likert scales, where 0=no pain and 4=extreme pain.

PTGA: Patient Global Assessment (Very well, well, Fair, Poor, Very poor)

COGA: Clinical Observer Global Assessment (Very well, well, Fair, Poor, Very poor)

Table 21. Secondary Categorical Efficacy Endpoints (proportional odds analysis) – ITT Population

	Synvisc-One n (%)	Control n (%)	Week 26 Estimate of Odds Ratio (95% CI)	Overall Estimate of Odds Ratio (95% CI)
PTGA	Week 26		0.51 (0.31, 0.82) p = 0.005	0.69 (0.50, 0.96) p = 0.029
Very Well	9 (7.3%)	2 (1.6%)		
Well	33 (26.6%)	27 (20.9%)		
Fair	50 (40.3%)	54 (41.9%)		
Poor	21 (16.9%)	31 (24.0%)		
Very Poor	2 (1.6%)	3 (2.3%)		
COGA	Week 26		0.56 (0.34, 0.93) p = 0.025	0.71 (0.50, 0.99) p=0.041
Very Well	13 (10.5%)	8 (6.2%)		
Well	37 (29.8%)	31 (24.0%)		
Fair	38 (30.6%)	38 (29.5%)		
Poor	22 (17.7%)	34 (26.4%)		
Very Poor	5 (4.0%)	6 (4.7%)		
WOMAC A1	Week 26		0.56 (0.35, 0.92) p = 0.022	0.64 (0.45, 0.91) p=0.013
None	17 (13.7%)	13 (10.1%)		
Mild	45 (36.3%)	39 (30.2%)		
Moderate	41 (33.1%)	42 (32.6%)		
Severe	11 (8.9%)	19 (14.7%)		
Extreme	1 (0.8%)	4 (3.1%)		

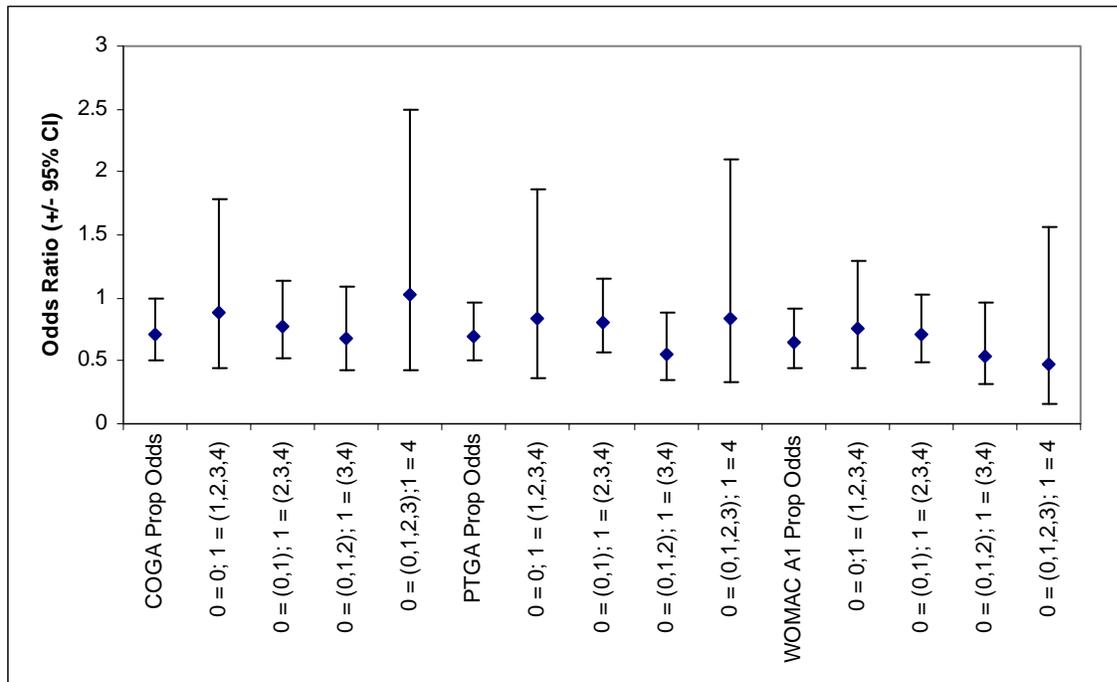
The applicant applied “Proportional odds models” or “Cumulative logit model” to analyze the above ordinal data (none, mild, moderate, severe, and extreme pain). Such statistical models require that the slopes of logit-transformed data be proportional based on different cutoff points for study covariates. The applicant should also address proportionality of slopes in their analyses.

Note: On November 10, 2008, during a teleconference between the applicant and FDA, the FDA raised the issue of the proportionality of slopes in the applicant's analyses as presented in Table 21.

The applicant responded and used the Generalized Estimating Equation (GEE) with the repeated measures for the ordered multinomial data using a proportional odds model. The applicant provided the following rationale regarding the acceptability of this approach:

“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.” This information is captured in Figure 1 below.

Figure 1. Chart for Proportional odds ratio for COGA, PTGA, and WOMAC 1



The applicant used a repeated-measure GEE model to claim significant odds ratios for the above three outcomes (e.g., WOMAC A1, PTGA and COGA). FDA was unable to verify the applicant’s proportionality odds model assumption (i.e., odds ratios are robust with respect to the selected cutoff points) due to a lack of the computer software program as the applicant to calculate the likelihood ratio test.

The applicant has provided a descriptive chart for all odds ratios based on the different cutoff points (Figure 1). As Figure 1 shows, most of these odds ratios are non-significant (e.g., the 2-sided 95% confidence intervals include unity), but combination of all data points over all visits showed significant odds ratios for the above three secondary outcomes.

FDA prepared Tables 22 and 23 to present these above data sets, combining this information into the following two by two tables.

Table 22. The estimated odds ratios (OR) for secondary efficacy endpoints, WOMAC A1 (Walking pain), at 26-week follow-up, ITT Population

Outcome	Synvisc-One	Placebo
Moderate + Severe + Extreme	53	65
None + Mild	62	52
Total	115	117
Odds ratio (OR)*: 0.68, 95% CI (0.41, 1.15), p=0.15		

* OR = $\frac{P[(\text{Moderate}+\text{Severe}+\text{Extreme})/P(\text{None}+\text{Mild}), \text{Synvisc}]}{[P(\text{Moderate}+\text{Severe}+\text{Extreme})/P(\text{None}+\text{Mild}), \text{Placebo}]} = (53/62)/(65/52) = 0.68$

Table 23. The estimated odds ratios for secondary efficacy endpoints, PTGA and COGA, at 26-week follow-up, ITT population

Outcome	Synvisc-One (PTGA)	Placebo (PTGA)	Synvisc-One (COGA)	Placebo (COGA)
Very well +Well	42	29	50	39
Fair + Poor +Very poor	= 73	88	65	78
Total	115	117	115	117
Odds ratio (95% CI)	0.57** (0.32, 1.01) p=0.053		0.65 (0.38,1.11) p=0.11	

** OR=[P(Fair+Poor+Very poor)/P(Very well+Well) for Synvisc-One]/P[(Fair+Poor+Very poor)/P(Very well+Well) for Placebo

Within Tables 22 and 23, for all three secondary efficacy endpoints (WOMAC A1, PTGA, COGA), their 95% confidence intervals include unity (all with non-significant p-values), at the 26-week follow-up. Synvisc-One failed to show superiority to Placebo with the above cutoff outcome points. Different cutoff outcome points or different visits will result in different odds ratios and their 95% confidence intervals. Further, Tables 21 and 22, calculated the odds ratios at Week 26, and combined the three worst outcomes (Moderate+Severe+Extreme) for WOMAC A1 (walking pain) versus the other two better outcomes (None pain +Mild pain), with non-significant odds ratios (odds ratio = 0.68, p=0.15), unadjusted by patient covariates. Similar non-significant results were demonstrated for PTGA and COGA.

The above FDA calculations are useful as supportive information about these secondary outcomes analyzed by the ordinal categorical data, other than those shown in Table 25, continuous data distribution by PROC MIXED model. Please note that: The PTGA, COGA and WOMAC C showed non-significant results by MIXED models.

The applicant also analyzed the responder rate using OMERACT-OARSI criteria. The results shown in Table 24 indicate that there was no statistically significant difference between Synvisc-One and the Placebo control at or over 26 weeks with respect to this endpoint.

Table 24. OMERACT-OARSI over all 26 weeks for the Responder Analysis

OMERACT-OARSI	Week 26		0.69 (0.41, 1.16) p = 0.156 at 26 weeks	0.66 (0.44, 1.02) p = 0.059 Over all
	Responder	Non-Responder		
Responder	73 (58.9%)	66 (51.2%)		
Non-Responder	50 (40.3%)	63 (48.8%)		
Based on Criteria	43	52		
Due to Withdrawal	7	11		

Applicant's Re-Analyses (in response to FDA's October 3, 2007 dated deficiency letter)

Since there were multiplicity issues associated with the secondary endpoints, the FDA also asked the applicant how they would adjust for type 1 error of the multiple endpoints (FDA's Major deficiency letter, dated 10/23/07). Within Amendment 4 of Supplement 12 (dated June 25, 2008), the applicant proposed hierarchical sequentially ordered testing for the following order:

1. WOMAC A1
2. PTGA

3. COGA
4. OMERACT-OARSI responders
5. WOMAC C

The hierarchical sequential fixed testing for the preceding order was provided by the Applicant in response to the FDA deficiency letter; this was not pre-specified in the protocol. The FDA believes it is only appropriate to proceed with secondary endpoints in the event the primary endpoint is determined to be both statistically and clinically meaningful.

Subsequent Re-Analyses Requested by FDA for the Secondary Endpoints

Since there were 21 sites in six European countries, FDA subsequently asked the applicant to analyze the secondary endpoints, using a mixed model of analysis of covariance (ANCOVA), which includes fixed and random effects in the statistical model, in the same manner as the primary endpoint was reanalyzed.

In Table 25, the results for the secondary endpoints using a mixed model for a longitudinal data analysis are presented. Results were based on repeated measures of a mixed model of ANCOVA including terms for treatment, site, time and time by-treatment interaction, as well as the baseline WOMAC Subscale A score as a covariate in the mixed model of analysis of covariance, and including site in the random effect.

Table 25. Analyses of Secondary Endpoints Requested by FDA
WOMAC LK 3.1 A Pain Subscore (Likert Scale) LSMEANS over 26weeks From Baseline – ITT
Population, using a mixed model of ANCOVA

	Synvisc -One (n=124) baseline	Placebo (n=129) baseline	Synvisc- One (n=124) (SE) LS mean	Placebo (n=129) (SE) LS mean	Estimated LS Difference in (Placebo – Synvisc-One) from baseline	2-sided 95% CI for the difference of two mean changes at	p-value
WOMAC LK A1 (pain on walking) overall 26 week	2.39	2.33	1.4437	1.6289	-0.1852 (0.07765)	- 0.3375 < δ < -0.328	0.0172
PTGA overall over 26 weeks	2.57	2.50	1.7720	1.9028	-0.1308 (0.07035)	- 0.2688 < δ < 0.0073	0.0633
COGA overall over 26 weeks	2.44	2.49	1.7793	1.9069	-0.1276 (0.0756)	- 0.2759 < δ < 0.0208	0.0918
WOMAC C overall 26 week	2.29	2.28	1.5761	1.6095	-0.03341 (0.07393)	- 0.1785 < δ < 0.1117	0.6515

* LS mean=LSMEANS :Least square mean

Note: Table 25 is from the reanalysis of the secondary endpoint using a mixed model of ANCOVA requested by FDA after the applicant’s response in Amendment 4 to FDA’s deficiency letter (dated October 31, 2007) was submitted. The above result is from the models which the FDA believes are most appropriate.

The results of these secondary endpoints were similar to that of the primary endpoint in terms of the size of the difference between Synvisc-One and Placebo control.

FDA will be asking the Panel a question about the secondary endpoints.

Labeling

Note to Panelists: The inclusion of a section on labeling in this memo should not be interpreted to mean that FDA has made a decision or is making a recommendation regarding the approvability of this PMA device.

The proposed Instructions for Use and Physician Instructions are included in the Panel Pack for your review (Refer to Section 7.0). Both of these documents include the following: 1) Description; 2) Indications; 3) Contraindications; 4) Warnings; 5) Precautions; 6) Storage and Handling, Instructions for Use 7) Information for Patients; 8) Use in Specific Populations; 9) Adverse events; 10) Summary of Clinical Studies and its results; 11) Device Description; 12) How supplied; 13) Direction for use; 14) Manufactured and Distributed by;

The applicant provided patient labeling (Refer to Section 7.0).

FDA will be asking the Panel a question related to this issue.

Post-Approval Study

Note to Panelists: FDA's inclusion of a section on a Post-Approval Study (PAS) in their Executive Summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The discussion of a post-approval study plan does not in any way alter the requirements for premarket approval. The recommendation from the Panel on whether to approve a device or not should be based on the premarket data, which must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered.

The applicant indicated that it did not provide a post-approval study (PAS) plan in the original PMA supplement due to the following considerations:

- 1) Synvisc-One is composed of the identical material (hylan G-F 20) as the currently marketed Synvisc, which has been shown to be well tolerated both locally and systemically.
- 2) The clinical evidence presented in this PMA/Supplement establishes the safety profile of Synvisc-One, which is similar to the Clinical and Post-marketing experience seen with Synvisc, where the treatment related adverse events (AEs) occurred with Synvisc-One were all mild to moderate in nature; and pain, swelling and effusion were the most frequently occurring AEs in the injected knee.
- 3) In addition, no new systemic AEs were identified with Synvisc-One as compared to the systemic AEs identified with Synvisc. Based on the fact that the Synvisc-One product merely combines the three injections 2mL per injection delivered at weekly intervals) of the currently marketed Synvisc into a single injection (6mL), in addition to ten years of clinical experience with Synvisc and the supporting clinical evidence in this PMA/Supplement, the applicant believes that a post-market study would not provide any additional assurance of safety that has not already been established by the existing evidence and therefore does not consider a post-approval study necessary at this time.

FDA identified a number of issues that may be considered in assessing the need for a PAS of Synvisc-One in the United States. The clinical study supporting this PMA supplement was conducted in Europe and the study population was limited to individuals of age 40 years or older. Studies have shown that patient's characteristics (such as body weight, age (<70 year), gender and time since diagnosis, etc.) may influence the treatment effects of the device^{1,2}. In addition, intra-articular injection of similar devices has demonstrated the treatment effects that can be extended to 12 months after the injection³, while the duration of follow-up of this study was only 26 weeks for the initial phase and 4 additional weeks for the repeat phase.

During the panel meeting, FDA will ask the Panel to comment on the possible need for a Post-Approval Study to address these and any other issues the panel thinks should be addressed, if the device is eventually approved. Again, the discussion of a PAS plan does not in any way alter the requirements for premarket approval. Please remember that recommendations from the Panel on whether or not to approve a device must be based on the premarket data.

FDA will be asking the Panel a question related to this issue.

¹ Kemper F, Gebhardt U, Meng T, et al. Tolerability and short-term effectiveness of hylan G-F 20 in 4253 patients with osteoarthritis of the knee in clinical practice. *Curr Med Res Opin.* 2005; 21(8): 1261-9

² Leopold SS, Redd BB, Warme WJ, et al. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee. A prospective, randomized trial. *J Bone Joint Surg Am.* 2003 ; 85-A(7): 1197-203

³ Clarke S, Lock V, Duddy J, et al. Intra-articular hylan G-F 20 (Synvisc) in the management of patellofemoral osteoarthritis of the knee (POAK). *Knee.* 2005; 12(1): 57-62