

Sponsor Summary for Synvisc-One

Center for Devices and Radiological Health (CDRH) Advisory Panel

Genzyme Corporation

December 9, 2008

Table of Contents

1.	Introduction.....	4
2.	Pivotal Trial Design and Results in Detail.....	8
2.1	Investigational Plan.....	8
2.2	Objective.....	8
2.3	Primary Endpoint.....	8
2.4	Secondary Endpoints	9
2.5	Study Design.....	9
2.6	Key Inclusion Criteria.....	10
2.7	Key Exclusion Criteria.....	11
2.8	Randomization	11
2.9	Follow-up Schedule	11
2.10	Pharmacovigilance.....	11
2.11	Statistical Design	12
2.11.1	Power and Sample Size.....	12
2.11.2	Efficacy Analyses	12
2.11.3	Control of Type I Error.....	13
2.12	Results.....	14
2.12.1	Disposition of Patients, Baseline Data.....	14
2.12.2	Primary Efficacy Results	16
2.12.3	Secondary Efficacy Results	20
2.12.4	Per-Protocol Analyses.....	24
2.12.5	Safety Results.....	24
2.12.6	Repeat Treatment Phase Safety Results.....	25
2.13	Summary of Pivotal Trial.....	26
3.	Evaluation of Effectiveness	27
3.1	Determining Clinical Meaning for OA Pain Relief Products.....	27
3.2	Clinical Meaning of Synvisc-One Results.....	28
3.3	Comparison of Synvisc-One with other FDA-approved products for treatment of OA pain.....	28
3.3.1	Improvement from Baseline	29
3.3.2	Effect Size.....	31
4.	Product History and Development: Synvisc-One.....	33
4.1	Product Description	33
4.2	Pre-clinical Development.....	34
4.3	The Safety and Effectiveness of Synvisc.....	34
4.4	Development of a Single-dose Regimen.....	35
4.5	Regulatory history.....	35
5.	FDA-Requested Re-analyses	37
6.	Risk-benefit Evaluation	38
7.	Conclusion	40
8.	References.....	41

List of Tables

Table 1: Overview of Key Results – ITT Population 7

Table 2: Baseline Characteristics – ITT Population 16

Table 3: Primary Efficacy: WOMAC A Pain Subscore Overall Change From Baseline – ITT Population 17

Table 4: Secondary Categorical Efficacy Endpoints – ITT Population 23

Table 5: Injected Knee Adverse Events during the Initial Treatment Phase: Safety Population 25

Table 6: Pharmaceutical Products for OA Pain Relief—WOMAC A 29

Table 7: Viscosupplement Products for Pain Relief—WOMAC A 30

Table 8: WOMAC A Effect Size – Comparison to Celecoxib 31

Table 9: Synvisc-One Syringe Contents 33

List of Figures

Figure 1: Study Flow Chart 15

Figure 2: Overall Change from Baseline WOMAC A (Pain) Score – ITT Population 18

Figure 3: Overall Estimated Change from Baseline WOMAC A (Pain) Score for Patients without Concomitant Symptomatic Lower Limb OA – ITT Population 19

Figure 4: Categorical Secondary Efficacy Endpoints – ITT Population 20

Figure 5: Continuous Secondary Efficacy Endpoints – ITT Population 21

Figure 6: WOMAC A1 Responder Rate – ITT Population 22

1. INTRODUCTION

Genzyme currently has a Pre-Market Approval Application (PMA) Supplement under review by the Office of Device Evaluation (ODE) within the Center for Devices and Radiological Health (CDRH) of the U.S. Food and Drug Administration (FDA) requesting authorization to distribute a modified version of the currently approved device, Synvisc® (hylan G-F 20). The modifications involve packaging and instructions for use and result in a device to be referred to as Synvisc-One.

Synvisc is a hyaluronic acid based viscosupplement that has been demonstrated to be safe and effective for the treatment of osteoarthritis (OA) pain of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics. The FDA approved treatment regimen includes three 2 mL intra-articular injections administered weekly.

The submission of this PMA supplement is an attempt to fulfill Genzyme's responsibility to provide adequate directions for use for physicians who elect to administer a single injection of Synvisc and to ensure that Synvisc continues to meet user and patient needs. The modification to Synvisc affords physicians and patients a convenient alternative to the treatment regimen described on the approved labeling to include a single intra-articular (IA) injection of 6 mL of Synvisc-One to treat OA of the knee. It was selected for pivotal clinical development based on the results of a pilot clinical study investigating various injection and volume regimens that showed that a 6 mL single injection performed at least as well as the currently-approved treatment regimen. The current Synvisc Package Insert can be found in Section 6 of this Panel Briefing Package and the proposed Synvisc-One™ Package Insert can be found in Section 7 of this Panel Briefing Package.

In order to confirm that Synvisc-One is safe and effective, a pivotal clinical trial was conducted. The pivotal clinical trial met its primary endpoint and the clinical results have been included in the PMA Supplement submission to FDA as evidence of the safety and effectiveness of this modified device. The fundamental question for the Panel is not whether Synvisc-One is safe, but whether it is effective, i.e., are the statistically significant reductions in pain, observed with Synvisc-One in the pivotal trial, clinically meaningful to patients. Genzyme and the Division of General, Restorative and

Neurological Devices (DGRND) in ODE have agreed to request Advisory Committee input on this issue.

The clinical data presented by Genzyme constitutes the highest level of valid scientific evidence required by FDA for regulatory decision-making. This evidence from the Synvisc-One clinical trial demonstrates that Synvisc-One met its pre-specified primary endpoint and provides a clinically meaningful result in a significant portion of the target population. Consider the following facts:

- The pivotal study was a randomized, controlled, patient and clinical observer blinded, multi-center trial involving 253 patients with mild to moderate knee OA. The study was conducted in accordance with GCP, ICH, and all applicable local laws and regulations.
- The pre-specified primary endpoint analysis of WOMAC A (pain) over 26 weeks demonstrated statistical superiority ($p=0.047$) to the control arm (arthrocentesis plus 6 mL of IA saline) in the Intent to Treat (ITT) population (all patients randomized).
- Synvisc-One was also statistically superior to the control arm in several key secondary endpoints measured over 26 weeks, including:
 - WOMAC A1 (pain on walking) ($p=0.013$)
 - Patient Global Assessment (PTGA) ($p=0.029$)
 - Clinical Observer Global Assessment (COGA) ($p=0.041$)
- Patients receiving Synvisc-One recorded a greater than 30% reduction in pain scores (from baseline) over 26 weeks ($p<0.001$). This is consistent with the literature on clinically important improvement in OA and with the treatment benefits shown by other approved pharmaceutical and medical device products for the treatment of OA pain. (See [Section 3.3](#))
- OA can affect multiple joints over the course of a trial and pain from other joints can affect overall assessment of pain. Within the ITT population a subset of patients was identified as those most likely to detect the effect of a local therapy; patients without concomitant symptomatic lower limb OA in the untreated joints. This analysis revealed a larger statistical superiority to the control arm in the primary endpoint (WOMAC A) ($p=0.012$). This covariate was pre-specified in

the statistical analysis plan, prior to unblinding, based on the knowledge that Synvisc-One is a local treatment. This analysis shows that the treatment effect is more evident in patients where pain from other joints is minimized.

The administration of a single 6 mL injection of Synvisc-One does not reveal any safety issues. In fact, the overall safety profile for Synvisc-One is comparable with the FDA approved three 2 mL injections of Synvisc. This trial constitutes valid scientific evidence that demonstrates that Synvisc-One is reasonably safe and effective for the treatment of pain associated with OA of the knee when used in accordance with the instructions and conditions of use as described in the proposed labeling. A single 6 mL injection of Synvisc-One provides clinically meaningful results in a significant portion of the target population.

Table 1 provides a complete listing of the results for all pre-specified primary and secondary endpoints. Complete details of the Study Design, Analyses and Outcomes are located in **Section 2**. This sponsor summary provides the following additional background information for panel member review:

- Detailed Pivotal Trial Design and Results (**Section 2**)
- Evaluation of Effectiveness (**Section 3**)
- Product Description for Synvisc and Synvisc-One (**Section 4**)
- Re-analyses Requested by FDA (**Section 5**)
- Risk Benefit Evaluation (**Section 6**)
- Conclusion (**Section 7**)
- References (**Section 8**)
- FDA Deficiency Questions (**Appendix 1**)

Table 1: Overview of Key Results – ITT Population

	Estimate of Treatment Difference (95% CI)	p-value
Primary Efficacy Endpoint		
WOMAC A ¹ (<i>Pain</i>)		
Change from baseline over 26 weeks*	-0.15 (-0.302, -0.002)	0.047
Secondary Efficacy Endpoints		
WOMAC A1 (<i>Pain</i>)		
Change from baseline at week 26	-0.18 (-0.372, 0.011)	0.064
WOMAC C ¹ (<i>Function</i>)		
Change from baseline over 26 weeks*	-0.03 (-0.18, 0.12)	0.679
Change from baseline at week 26	-0.11 (-0.31, 0.09)	0.266
Estimate of Odds Ratio² (95% CI)		
WOMAC A1 (<i>Walking Pain</i>)		
Over 26 weeks*	0.64 (0.45, 0.91)	0.013
At week 26	0.56 (0.35, 0.92)	0.022
PTGA (<i>Patient Global Assessment</i>)		
Over 26 weeks*	0.69 (0.50, 0.96)	0.029
At week 26	0.51 (0.31, 0.82)	0.005
COGA (<i>Blinded Observer Assessment</i>)		
Over 26 weeks*	0.71 (0.50, 0.99)	0.041
At week 26	0.56 (0.34, 0.93)	0.025
OMERACT-OARSI responder criteria		
Over 26 weeks*	0.66 (0.44, 1.02)	0.059
At week 26	0.69 (0.41, 1.16)	0.156

*Over 26 weeks - repeated measures analysis including efficacy data from weeks 4, 8, 12, 18, and 26

¹ WOMAC Questions were collected via a 0-4 Likert Scale and are shown as averages of the responses for each subscale.

² Odds ratios of <1 favor the active treatment, Synvisc-One.

2. PIVOTAL TRIAL DESIGN AND RESULTS IN DETAIL

“SYNV00704: A Multi-centre, Parallel, Double-Blind, Blinded Evaluator, Randomised, Placebo-Controlled Evaluation of the Efficacy and Safety of a Single Dose of 6 mL of Synvisc in Patients with Symptomatic Osteoarthritis of the Knee”

2.1 Investigational Plan

The study was conducted at 21 sites in Europe (4 Belgium, 4 Czech Republic, 5 France, 1 Germany, 2 Netherlands and 5 United Kingdom) in two phases:

- An initial treatment phase evaluating safety and efficacy over a 26-week follow-up period, and
- A repeat treatment phase to evaluate the safety of a second injection of Synvisc-One over a period of 4 weeks.

The trial included 253 patients with symptomatic primary OA of the knee. The first patient visit was on May 29, 2005. The last patient visit was on September 28, 2006.

The protocol was designed and was conducted, recorded, and reported in compliance with the principles of GCP guidelines established by the basic principles defined in the U.S. 21 CFR Part 312 and ISO 14155, as well as in accordance with all national, state, and local laws of the appropriate regulatory authorities and the Declaration of Helsinki (October 1996). The GCP guidelines are stated in the “Guidance for Good Clinical Practice,” International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

2.2 Objective

To compare the safety and efficacy of 1 x 6-mL IA injection of Synvisc against 1 x 6-mL IA injection of Saline Control (phosphate-buffered saline [PBS]) in treating patients with symptomatic primary OA of the knee.

2.3 Primary Endpoint

The primary efficacy endpoint was to demonstrate that a 1 x 6-mL injection of Synvisc provides superior pain relief over 26 weeks as compared to a 1 x 6-mL IA injection of saline control in treating patients with symptomatic primary OA of the knee. The

principal outcome instrument was the WOMAC, Likert Version 3.1. The primary variable was the average score of the five WOMAC A (pain) subscale questions: “How much pain have you had... 1) when walking on a flat surface? 2) when going up or down stairs? 3) at night while in bed? (that is - pain that disturbs your sleep) 4) while sitting or lying down? 5) while standing?” (Bellamy, 1988, *J Rheumatol*) Patients responded using a 5-point adjectival Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme).

2.4 Secondary Endpoints

Supportive analyses included analyzing the differences between the following secondary endpoints over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc-One treatment group and the saline control group:

- Question 1 of the WOMAC A (pain while walking on a flat surface)
- Subscale C of the WOMAC (function)
- Patient Global Assessment (PTGA) of disease severity (“Considering all the ways that the arthritis of your target knee affects you, select one response below for how you are doing at the present time: 0 = very well, 1 = well, 2 = fair, 3 = poor, 4 = very poor”)
- Clinical Observer Global Assessment (COGA) of disease severity (“Make a global assessment of the patient's disease status by marking an (X) in one box below: 0 = very well, 1 = well, 2 = fair, 3 = poor, 4 = very poor”)
- OMERACT-OARSI Responder (a patient is classified as a positive responder if the patients has a large improvement in pain (WOMAC A) or function (WOMAC C), or a smaller improvement in at least 2 of pain (WOMAC A), function (WOMAC C) or PTGA)

2.5 Study Design

At the screening visit, a physical examination and radiographic assessment of the target knee was performed.

The patient began the “washout” period of prohibited medications (i.e., those with half-lives of > 5 hours); from that point forward, none of the prohibited medications was to be

taken at any time during the study. The washout period lasted for up to 21 days, depending on the half-life of the medications. Rescue medication for the injected knee consisted of acetaminophen (up to 4000 mg/day); however, for 48 hours prior to study visits, patients were to forego acetaminophen and any other pain or OA medications that were otherwise permitted during the study (e.g., analgesics/NSAIDs with a half-life \leq 5 hours for indications other than OA pain, not to be taken for more than 5 consecutive days or $>$ 10 days per month; and aspirin (\leq 325 mg per day)).

Synvisc-One was supplied as a 6.0 mL injection. The saline control consisted of 6.0 mL of phosphate-buffered saline, identical to that used as diluent in the Synvisc-One manufacturing process. Both Synvisc-One and saline control treatments were provided as a 6-mL fill volume in a 10-mL glass syringe, packaged identically in order to maintain the study blind.

The blinded patient completed the required questionnaires (WOMAC and PTGA), and a blinded evaluator (i.e., different from the unblinded injector) completed the COGA. Safety assessments included recording physical examination findings (including injected knee), concomitant medications and treatments, vital signs. Adverse events were collected and reported from the time the patient signed the informed consent until study completion. For each injected knee AE, the clinical observers were asked whether or not the event was related to the study procedure (i.e., expected with any IA injection procedure) and whether or not the event was related to the study treatment (i.e., study material).

In order to assess the safety of a repeat injection of 6 mL of Synvisc-One, patients from both groups were permitted to enter a four-week open-label repeat treatment phase 26 weeks after their initial study injection if they had no major safety concerns during the first course of treatment and had an average WOMAC A score of at least one.

2.6 Key Inclusion Criteria

All patients met the American College of Rheumatology (ACR) criteria for OA (Altman, 1986, Arthritis Rheum). Main initial treatment phase inclusion criteria were: 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; and a mean score of 1.5 to 3.5 on all five questions of the WOMAC subscale A.

2.7 Key Exclusion Criteria

Main initial phase exclusion criteria were: 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.

2.8 Randomization

Eligible patients were randomized to one of two treatment arms: arthrocentesis followed by a 6-mL IA injection of Synvisc-One, or arthrocentesis followed by a 6-mL IA injection of saline control. Randomization was performed via a centralized interactive voice-response system, and was done by site in computer-generated blocks of four. Unblinded injectors were strictly forbidden from discussion of treatment allocation with either patients or clinical observers.

2.9 Follow-up Schedule

Patients had scheduled visits at 1, 4, 8, 12, 18, and 26 weeks following injection. 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.

2.10 Pharmacovigilance

The safety analyses were performed on the safety population defined as all patients who underwent the first injection. Treatment-emergent AEs were summarized by treatment group and categorized by severity and relationship to the study procedures. Target knee AEs also were summarized separately. 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 or study treatment, was indicated in cases of multiple occurrences

of the same AE. All AEs were presented in a listing. Additionally listings of serious adverse events (SAEs) and AEs leading to discontinuation were generated.

Vital signs and physical examination findings were tabulated. Concomitant medications and treatments were categorized using a standardized coding dictionary (e.g., Medical Dictionary for Regulatory Activities [MedDRA], World Health Organization Drug Dictionary [WHO-drug]) and summarized. For the Repeat Treatment Phase of the study, all treatment-emergent AEs were summarized.

2.11 Statistical Design

The statistical analyses were prospectively defined in the statistical analysis plan prior to database lock and unblinding.

2.11.1 Power and Sample Size

The sample size estimation was based on the mean difference in the WOMAC A pain subscale change from baseline over 26 weeks. The following assumptions were made to compute the sample size: common standard deviation (SD) of 0.725; dropout rate of 25%; and a 2-sided significance level of 5%. With these assumptions, a sample size of approximately 250 patients (125 patients per arm) provided over 80% power to detect a difference of 0.297 between the Synvisc-One and control groups over 26 weeks.

2.11.2 Efficacy Analyses

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 analysis of covariance (ANCOVA) that was used to test for differences in treatment efficacy, as quantified by the WOMAC A (pain) subscore over 26 weeks between Synvisc-One and control. The ANCOVA model included terms for treatment, site, time and time-by-treatment interaction, as well as the baseline WOMAC A score as a covariate.

Secondary efficacy analyses included the difference between the Synvisc-One and control groups from baseline to week 26 in WOMAC A, and the differences from baseline over 26 weeks and from baseline to week 26 in WOMAC A1, WOMAC C (Physical Function), PTGA, COGA, and the responders to treatment per the Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International

(OMERACT-OARSI) responder criteria (Pham, 2004, *Osteoarthritis Cartilage*.) For WOMAC A and WOMAC C, a repeated-measures ANCOVA was used as described for the primary efficacy analysis.

WOMAC A1, PTGA, COGA were analyzed using generalized estimating equations (GEE) for repeated binary outcomes and GEE proportional odds logistic regression. OMERACT-OARSI responders were analyzed using generalized estimating equations (GEE) for repeated binary outcomes. These are methods commonly used for dichotomous and multinomial outcomes collected at several visits over the course of a study. 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 estimated proportional odds ratio.

- An odds ratio of 1 indicates that a positive response is equally likely in both groups.
- An odds ratio greater than 1 indicates that a positive response is less likely in the Synvisc-One group and an odds ratio less than 1 indicates that a positive response is more likely in the Synvisc-One group.
- The further away from 1 the greater the treatment effect

2.11.3 Control of Type I Error

This study protocol was written with reference to ICH E9. ICH E9 states “When multiplicity is present, the usual frequentist approach to the analysis of clinical trial data may necessitate an adjustment to the Type I error. Multiplicity may arise, for example, from multiple primary variables, multiple comparisons of treatments, repeated evaluation over time and/or interim analyses.” In this study, the only one of these conditions present was the repeated evaluation over time. In order to maintain the overall Type I error the overall change from baseline was calculated for the primary endpoint.

FDA has questioned the fact that Genzyme did not pre-specify an adjustment for multiplicity of secondary endpoints. Because these analyses are considered supportive to the primary analysis (i.e., not required to demonstrate efficacy of the test article), there is no requirement under ICH to adjust for multiplicity. The review division expressed

concern that the statistical significance observed in a number of secondary endpoints occurred by chance alone. In order to address this Genzyme performed a re-sampling method to address the hypotheses that any 3 of the 5 secondary endpoints (WOMAC A1, PTGA, COGA, OMERACT–OARSI Responders, and WOMAC C) were statistically significant at the 5% level was incompatible with chance. Genzyme simulated the study 20,000 times, each time with a different permutation of the randomization and re-analyzed these 5 secondary endpoints. These simulations resulted in the finding that the probability of observing the 3 statistically significant secondary endpoints (WOMAC A1, PTGA, and COGA) due to chance alone was only 3.94%.

2.12 Results

2.12.1 Disposition of Patients, Baseline Data

Three hundred twenty-nine patients enrolled; 76 patients (23.1%) were screening failures. A total of 253 patients (73 men, 180 women) from 21 study centers were randomized and analyzed for the initial treatment phase of the study: 124 to receive Synvisc-One and 129 to receive control. All 253 randomized patients were included in the safety population (Synvisc-One: 123 patients; control: 130 patients). One patient was randomized to the Synvisc-One group but inadvertently received saline control in error and was therefore counted in the control group for safety and the Synvisc-One group for ITT efficacy. A total of 232 patients (91.7%) completed the study. Nine patients (7.3%) randomized to Synvisc-One and 12 patients (9.2%) randomized to control failed to complete the study schedule as planned (**Figure 1**). There were no clinically meaningful differences between treatment groups in any baseline or demographic parameter (**Table 2**). In particular, baseline WOMAC A values were similar between groups.

Figure 1: Study Flow Chart

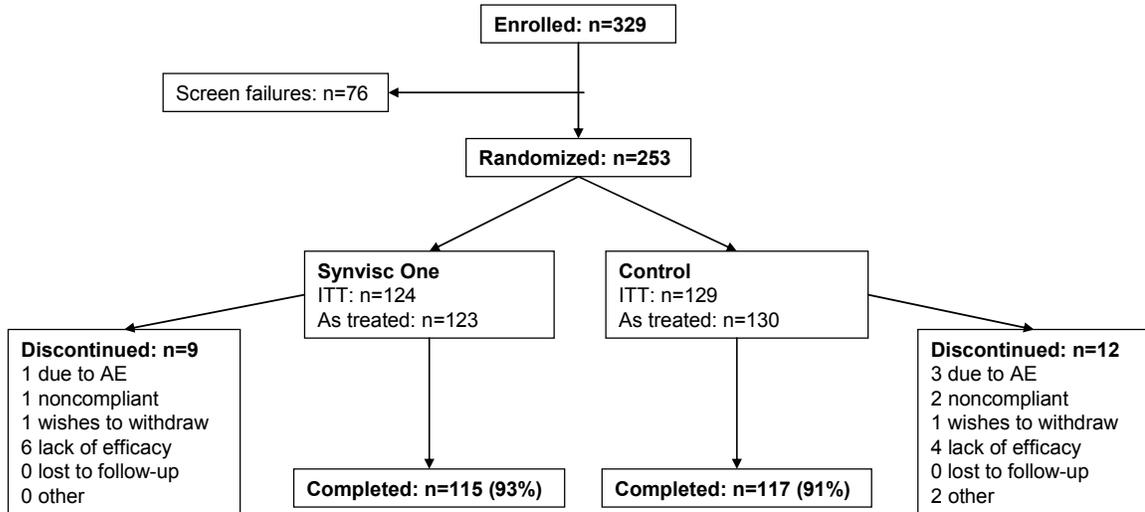


Table 2: Baseline Characteristics – ITT Population

	Synvisc-One (N=124)	Control (N=129)
Age (years)	63.6 (9.64)	62.5 (9.17)
BMI (kg/m ²)	29.08 (4.8)	29.77 (5.7)
Sex, (M/F)	32/92	41/88
Race, n (%)		
Caucasian	118 (95.2)	125 (96.9)
Non-Caucasian	6 (4.8)	4 (3.1)
Tibio-femoral compartment with the most severe features of OA, n* (%)		
Medial	93 (75.6)	103 (79.2)
Lateral	30 (24.4)	27 (20.8)
Modified Kellgren-Lawrence grade in most severe tibio-femoral compartment, n* (%)		
Grade II	63 (51.2)	51 (39.2)
Grade III	60 (48.8)	78 (60.0)
Grade IV	0	1 (0.8)
Prior corticosteroids in injected knee, n*		
Yes – n (%)	40 (32.5)	31 (23.8)
Prior arthroscopy in injected knee, n*		
Yes – n (%)	26 (21.1)	28 (21.5)
Total WOMAC score (0-96); Mean (SD)	55.1 (10.5)	54.8 (9.4)
WOMAC A score (0-4); Mean (SD)	2.30 (0.426)	2.25 (0.41)
Symptomatic OA that was responsive to acetaminophen and did not require other therapy, n* (%)		
In the contralateral knee	68 (55.3)	76 (58.5)
In either hip	12 (9.8)	18 (13.8)
Mean time since OA diagnosis, months* (median, range)	77.4 ± 76.4 (51.9, 3.1 to 350.9)	70.0 ± 64.4 (47.3, 3.6 to 241.9)

Values are mean (SD) or number and percentage of patients unless otherwise specified.

*Safety population

2.12.2 Primary Efficacy Results

The treatment effect with Synvisc-One was statistically significantly superior to control for the primary endpoint, WOMAC A over 26 weeks (inter-group difference: 0.15, p=0.047; [Table 3](#)). The Baseline mean WOMAC A average score was 2.30 (SD 0.426;

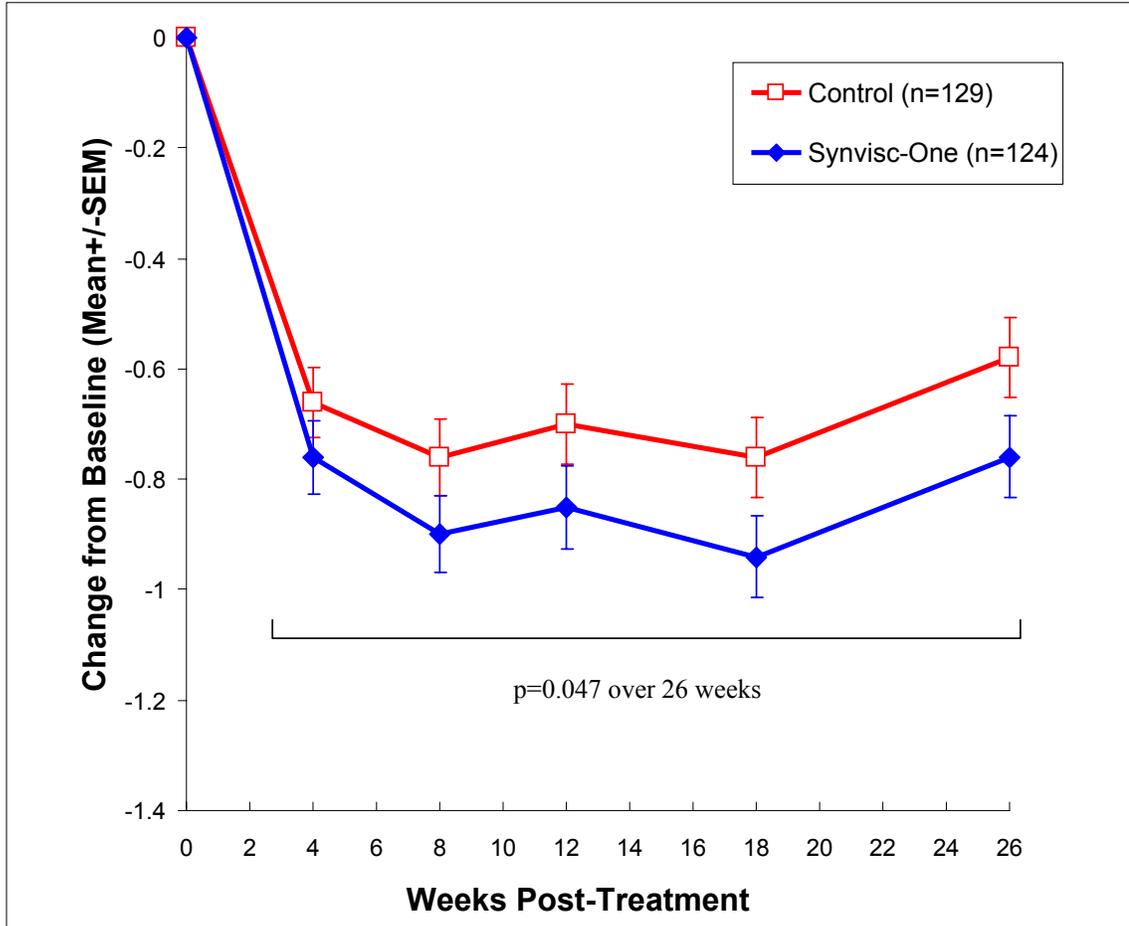
median = 2.20, range: 1.6, 3.4) for the Synvisc-One group, and 2.25 (SD 0.410; median = 2.20, range: 1.6, 3.4) for the control group. Synvisc-One demonstrated a change from baseline over 26 weeks of -0.84 (Standard Error 0.060), which is a 35.8% reduction in pain from baseline.

Table 3: Primary Efficacy: WOMAC A Pain Subscore Overall Change From Baseline – ITT Population

	Baseline Mean (SE)	Overall Mean (SE)	Estimated Change (SE)	Estimated Difference from Control (95% CI)	p-value
Synvisc-One (n=124)	2.30 (0.038)	1.43 (0.060)	-0.84 (0.060)	-0.15 (-0.3021, -0.0023)	0.047
Control (n=129)	2.25 (0.036)	1.59 (0.058)	-0.69 (0.058)		

Patients in the saline control group had a greater-than-expected change from baseline over 26 weeks of -0.69, a 28.7% reduction in pain from baseline. Results were based on repeated measures 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 95% confidence interval around the estimated treatment difference is -0.3021 to -0.0023 and does not include zero. **Figure 1** presents the change in WOMAC A over the entire initial treatment phase of the study.

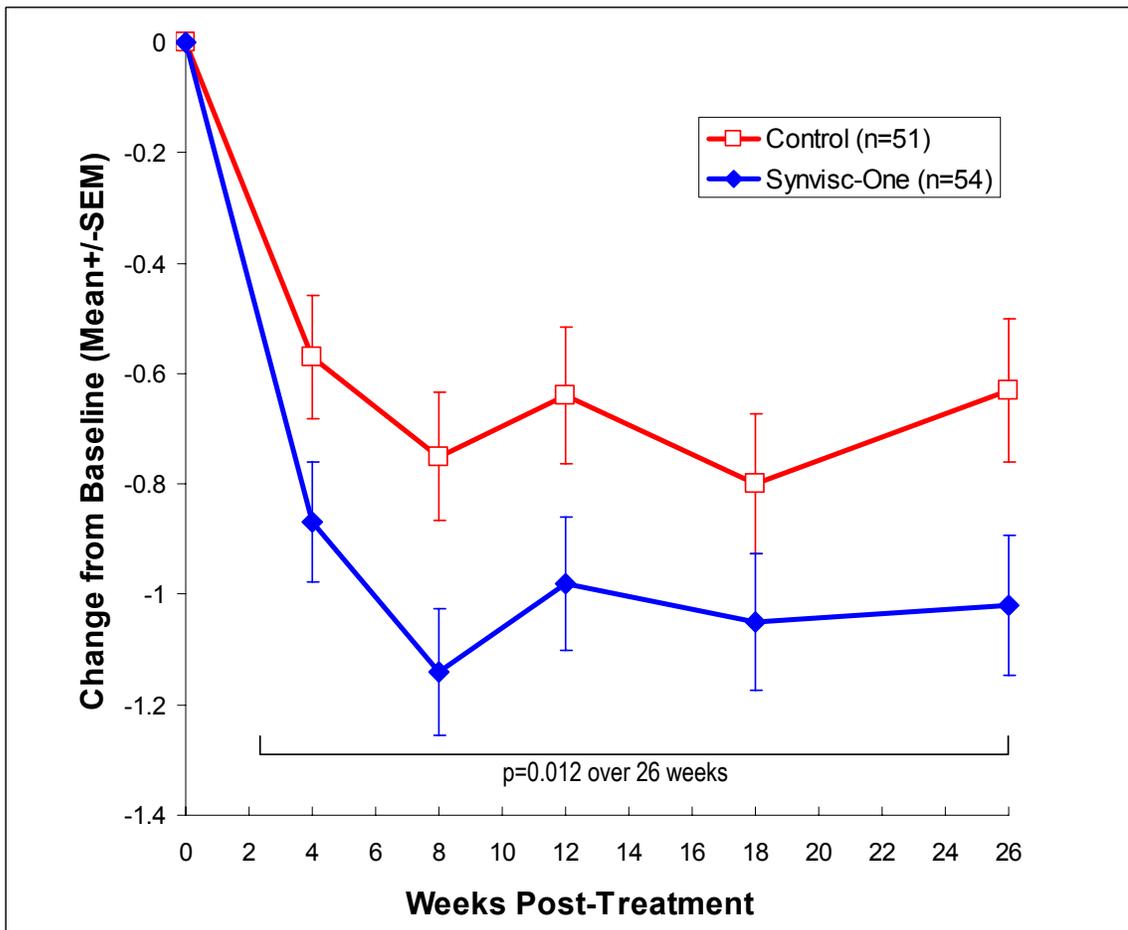
Figure 2: Overall Change from Baseline WOMAC A (Pain) Score – ITT Population



* The WOMAC A component description is provided in [Section 2.3](#).

The analysis of WOMAC A for a pre-defined covariate (patients without concomitant symptomatic lower limb OA) further supports the primary endpoint results. In these patients there was a larger difference in pain relief favoring patients who received Synvisc-One (-0.33, p=0.012).

Figure 3: Overall Estimated Change from Baseline WOMAC A (Pain) Score for Patients without Concomitant Symptomatic Lower Limb OA – ITT Population



* The WOMAC A component description is provided in [Section 2.3](#).

2.12.3 Secondary Efficacy Results

Of the secondary endpoints, the WOMAC A1 (pain on walking), PTGA and COGA showed statistically significant differences between the two study groups in favor of the patients who received Synvisc-One (**Table 4**).

Figure 4 is an odds-ratio plot of the clinical results for the categorical secondary endpoints in the Synvisc-One pivotal clinical trial. All 8 of the pre-specified categorical secondary endpoint analyses had estimates in favor of Synvisc-One; 6 out of 8 of these demonstrated a statistically superior reduction in symptoms and significant differences in global assessments favoring Synvisc-One.

Figure 4: Categorical Secondary Efficacy Endpoints – ITT Population

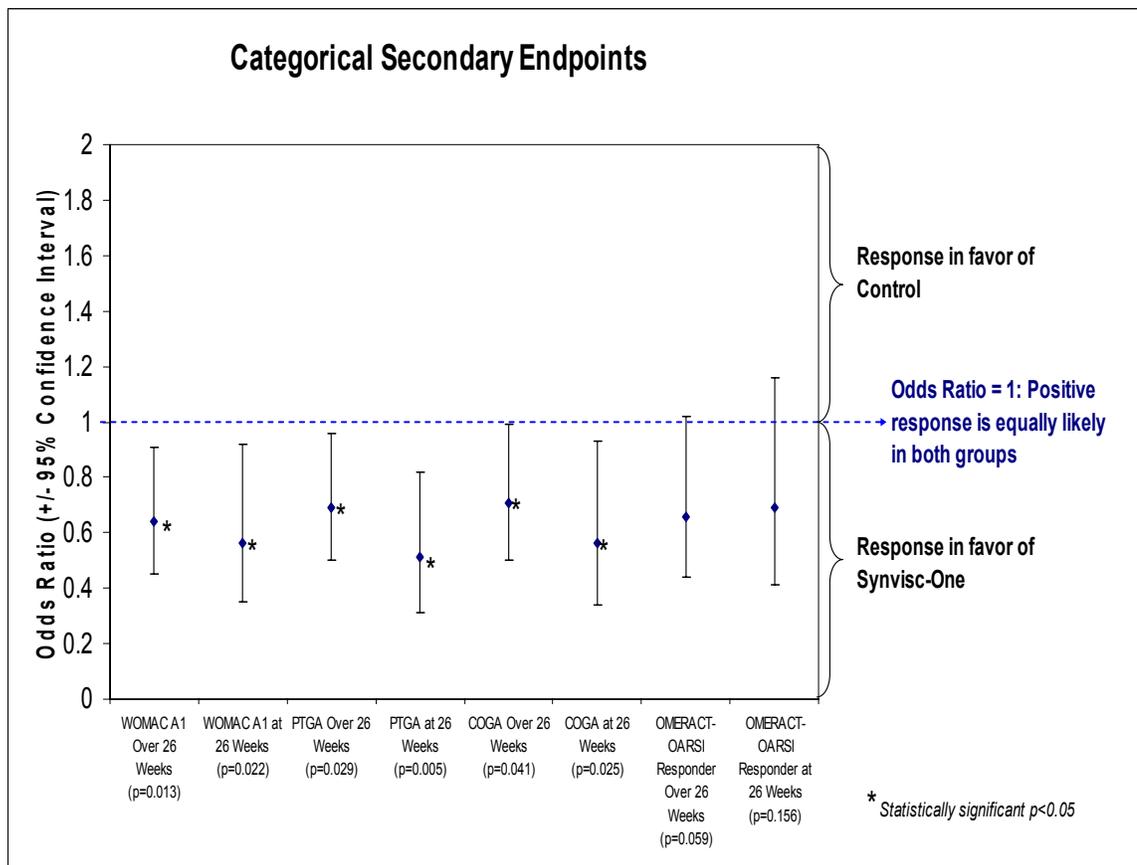
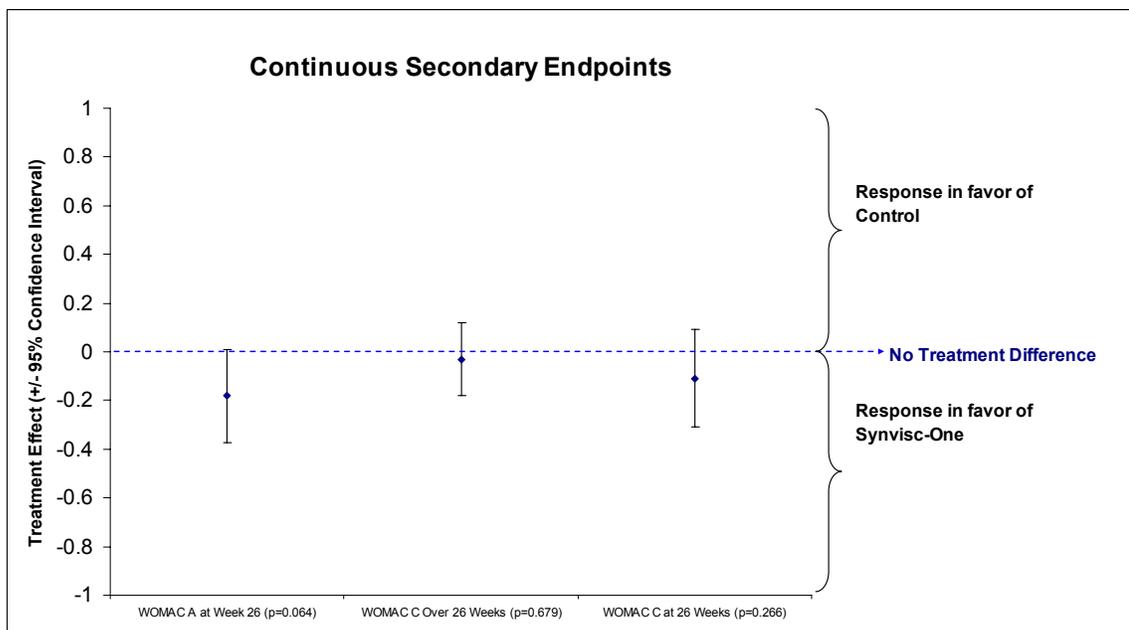


Figure 5 is an odds-ratio plot of the clinical results for the continuous secondary endpoints in the Synvisc-One pivotal clinical trial. Figure 5 shows the results for WOMAC A at 26 weeks and for WOMAC C over 26 weeks and at 26 weeks. While WOMAC A at 26 weeks, WOMAC C and OMERACT-OARSI secondary endpoints were not met statistically, these endpoints all trended in favor of Synvisc-One.

Figure 5: Continuous Secondary Efficacy Endpoints – ITT Population

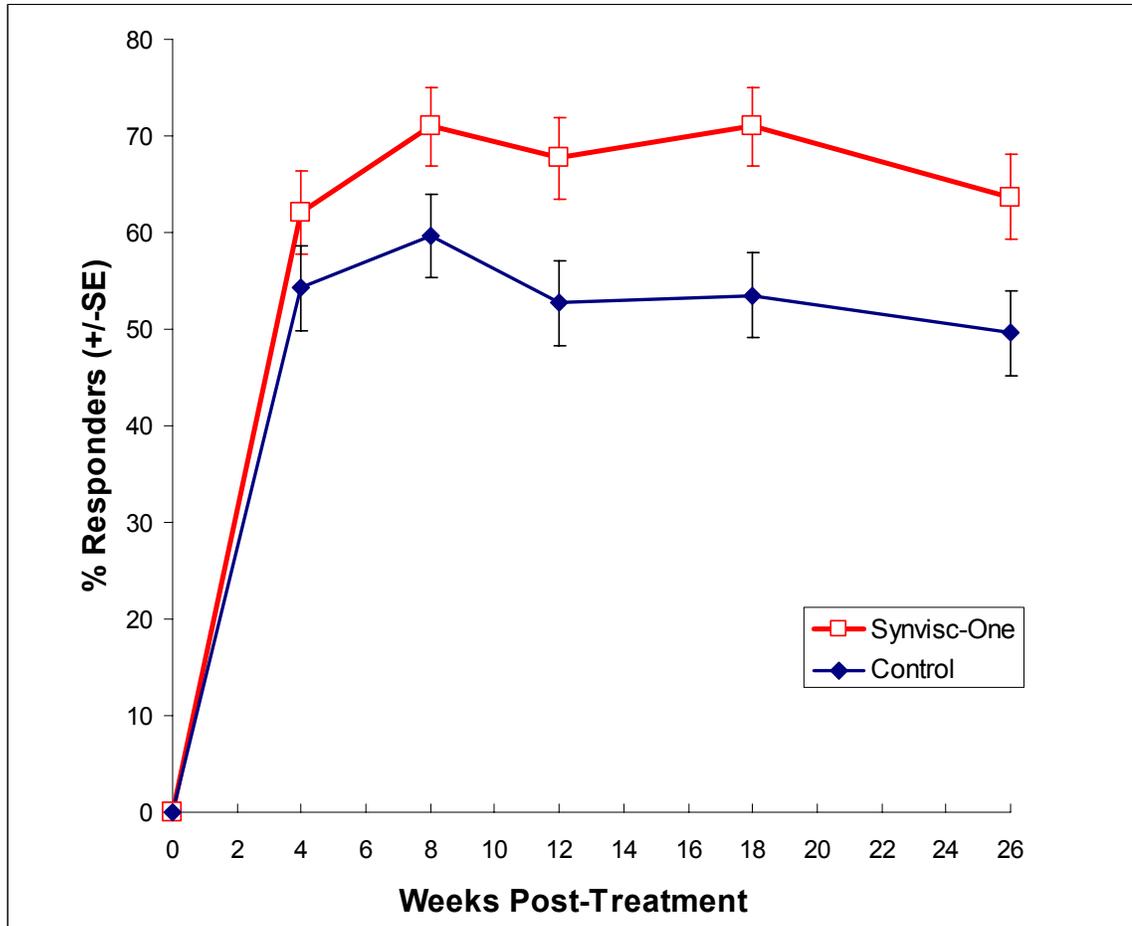


A WOMAC A1 responder was defined as a patient who improved by at least one category on the Likert Scale and did not withdraw from the study due to lack of efficacy.

Figure 6 illustrates the WOMAC A1 responder rate: 71.0% of the patients were responders at week 18 in the Synvisc-One group (versus 53.5% in the control group, $p=0.003$). At week 26, 63.7% of patients in the Synvisc-One group were responders (versus 49.6% in the control group, $p=0.028$).

WOMAC A1 (pain on walking) is a commonly used outcome measure for local therapies for OA of the knee. Patients with earlier stage knee OA often present clinically with this symptom, whereas pain at night or while sitting or lying (other questions on WOMAC A) tend to manifest more in patients with late or endstage OA.

Figure 6: WOMAC A1 Responder Rate – ITT Population



The change in WOMAC C (function) scores did not show statistical significance. Further exploratory analyses of covariates were carried out to better understand the results. The effect was greater in patients treated with Synvisc-One who did not have any other lower limb OA. However, an alternative explanation is that it takes time and a dedicated effort to improve function, and such efforts were not incorporated in the trial

The OMERACT-OARSI Responder Analyses approached statistical significance over 26 weeks; the observed differences were consistently in favor of Synvisc-One (odds ratio [control/Synvisc-One] 0.66, p = 0.059).

Table 4: Secondary Categorical Efficacy Endpoints – 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%)		
OMERACT-OARSI	Week 26		0.69 (0.41, 1.16) p = 0.156	0.66 (0.44, 1.02) p = 0.059
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		

There was a slightly higher average consumption of rescue medications in the control arm. This difference became more apparent at the end of the trial and by Week 26 the reduction in use of acetaminophen in the Synvisc-One group compared to the control group trended towards statistical significance (p=0.086).

2.12.4 Per-Protocol Analyses

Separate analyses have been done excluding subjects with protocol violations that could have impacted the evaluations. These per-protocol analyses were supportive of the results obtained in the ITT population.

2.12.5 Safety Results

There were no target knee Serious Adverse Events (SAEs), nor were there any SAEs which were assessed by the Investigator to be related to study treatment or study procedure (i.e., IA injection procedure). The overall number of patients with an AE during the initial treatment Phase of the study (Synvisc-One: n=70, 56.9%; saline control: n=79, 60.8%) and with a target knee AE (Synvisc-One: n=44, 35.8%; saline control: n=44, 33.8%) was comparable between 2 treatment groups. The most commonly reported AEs after IA injection of Synvisc-One or control were pain in the injected knee (coded as “arthralgia”), joint stiffness, joint effusion and joint swelling (**Table 5**). The number of patients with AEs that were assessed by the Investigator to be study procedure-related was 5.7% for the Synvisc-One group and 3.8% for the saline control group. Most importantly, the number of patients with AEs that were assessed by the Investigator to be study treatment-related was 3.3% for the Synvisc-One group and 1.5% (n=2) for the saline control group. These findings are comparable to current labeling for Synvisc 3 x 2 mL where the incidence of target knee AEs is 7.2%. All treatment-related and procedure-related target knee AEs were of mild or moderate severity and were of a type consistent with the known safety profile of Synvisc-One (e.g. arthralgia, injection site pain).

Table 5: Injected Knee Adverse Events during the Initial Treatment Phase: Safety Population

Preferred Term	Synvisc-One N = 123 n (% of patients)	Control N = 130 n (% of patients)
Any treatment-emergent injected knee adverse event	44 (35.8)	44 (33.8)
Any treatment- and/or procedure-related injected knee AEs (Preferred terms below)	7 (5.7)	4 (3.1)
Arthralgia	2 (1.6)	3 (2.3)
Joint effusion	2 (1.6)	0 (0)
Arthritis	1* (0.8)	0 (0)
Arthropathy	1 (0.8)	0 (0)
Injection site pain	1 (0.8)	1 (0.8)
Any treatment-related injected knee AEs	4 (3.3)	1 (0.8)
Any procedure-related injected knee AEs	6 (4.9)	4 (3.1)

* Patient withdrew from the study due to injected knee arthritis of moderate severity.

2.12.6 Repeat Treatment Phase Safety Results

A separate evaluation of safety on repeat injection was carried out after all efficacy evaluations were completed. One hundred sixty patients were treated, of which 77 patients received a second injection of Synvisc-One and 83 patients received a first injection of Synvisc-One after receiving a saline control injection during the initial treatment phase.

The safety profile in the Repeat Treatment Phase of the study was similar to the initial phase. No target knee serious AEs occurred. One patient who was in the control group in the initial phase and who received Synvisc-One in the repeat treatment phase had a severe, unrelated SAE of acute myeloid leukemia (AML), deemed by the Investigator as not related to the study treatment or procedure. In the group receiving a second injection of Synvisc-One there was one patient (1.3%) who experienced target knee AEs assessed as related to the study treatment and four patients (5.2%) who experienced target knee AEs related to the injection procedure. 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 on repeat exposure to Synvisc-One.

In summary, the most frequent target knee AEs were knee pain (arthralgia) and injection site pain. All related target knee AEs were of mild or moderate severity, and repeat exposure did not affect the safety profile.

2.13 Summary of Pivotal Trial

The Synvisc-One clinical study demonstrated a statistically significant difference between the two groups in the patient's assessment of pain on the WOMAC pain subscale (WOMAC A) over 26 weeks for the ITT Population. The change from baseline over 26 weeks on the mean WOMAC A Likert score is -0.84 in the Synvisc-One group and -0.69 in the saline control group. The difference between the two treatment groups is statistically significant (-0.15, $p=0.047$). Furthermore, the Synvisc-One clinical data show that to patients, this treatment resulted in a 35.8% improvement from baseline in WOMAC A over 26 weeks, exceeding the 20% change identified in the literature as the minimum clinically important improvement (MCII) and therefore showing a clinically meaningful improvement.

The primary efficacy endpoint was supported by multiple secondary endpoints indicating a superior outcome with Synvisc-One. Importantly, the endpoints were evaluated by either a clinical observer or the patients themselves, both of which were unaware of treatment assignment.

Evaluation of the safety profile for the higher injected volume (6 mL) of Synvisc-One was another objective of this study. Synvisc-One showed a comparable safety profile to saline control following initial and repeat treatment. No new AE(s) were identified with one injection of 6 mL of Synvisc-One during this study as compared to the current product information (pain, swelling, effusion) and the incidence remained unchanged.

3. EVALUATION OF EFFECTIVENESS

There are numerous pharmaceuticals and medical devices approved in the U.S. to treat osteoarthritis, and the literature on this topic is vast. Clinical practice guidelines recommend use of these products, including several viscosupplements (e.g., American Academy of Orthopaedic Surgeons [AAOS]; American College of Rheumatology [ACR] & American Pain Society [APS]). In assessing the effectiveness of Synvisc-One, it is important to consider the device's effect within the context of the clinical contributions of all FDA regulated products for pain relief in osteoarthritis. Furthermore, the device's effectiveness must be determined based on valid scientific evidence that shows that the device provides clinically significant results in a significant portion of the target population as stated in the regulations.

3.1 Determining Clinical Meaning for OA Pain Relief Products

Experts have defined the minimum clinically important improvement (MCII) in numerous publications. For example, "...the smallest difference in score (i.e., the effect) reported by patients that correlates with the patient stating that he or she is 'slightly better' compared to his or her own state at an earlier point" (Salaffi, 2004, *Eur J Pain*). The definitions are consistent among authors and together establish an expert consensus definition of MCII (Tubach, 2004, *Ann Rheum Dis*; Kvien, 2007, *Ann Rheum Dis*; Tubach, 2007, *J Rheumatol*). Published experts also concur that clinical meaning for a primary endpoint in an OA pain study should be determined based on within-group responses using the MCII, and not between groups (Bellamy, 2001, *J Rheumatol*; Farrar, 2001, *Pain*; Salaffi, 2004, *Eur J Pain*; Tubach, 2005, *J Rheumatol*; Copay, 2007, *Spine J*; Kvien, 2007, *Ann Rheum Dis*).

The scientific and medical literature on MCII for pain describes threshold ranges from 15% to 20% improvement from baseline as clinically meaningful. Recently published values for MCII in OA and other musculoskeletal conditions reported as a percent improvement from baseline include:

- A 12% to 18% improvement in WOMAC A for OA (prospective cohort studies) (Angst, 2001, *Arthritis Care Res*; Angst, 2002, *J Rheumatol*).

- A 15% improvement in a numerical rating scale for chronic musculoskeletal pain intensity (prospective cohort study) (Salaffi, 2004, *Eur J Pain*).
- A 20% improvement in pain, patient global assessment and function in rheumatic diseases (Outcome Measures in Rheumatology [OMERACT] Special Interest Group Consensus Survey) (Tubach, 2007, *J Rheumatol*).
- A 20% improvement in a numerical rating scale for OA pain (Arnold, 2007, presented at American Academy of Neurology).
- A 10% to 20% improvement in chronic pain (IMMPACT Consensus Statement) (Dworkin, 2008, *J Pain*).

In summary, the consensus of these literature reports supports a conservative MCII threshold of 15-20% in OA pain.

3.2 Clinical Meaning of Synvisc-One Results

In comparison to the literature, the Synvisc-One clinical study revealed a 35.8% improvement from baseline for WOMAC A ($p < 0.001$) in patients treated with Synvisc-One over 26 weeks and a 31.3% improvement from baseline ($p < 0.001$) in patients treated with Synvisc-One at Week 26 in the ITT population. The improvement in WOMAC A scores from baseline for Synvisc-One surpasses the thresholds identified for MCII in the literature and is in alignment with patient global improvement ratings of “much better,” and “much improved” or “very much improved” (approximately 30% improvement from baseline).

3.3 Comparison of Synvisc-One with other FDA-approved products for treatment of OA pain

A variety of other products are currently available for the treatment of OA related pain. These include:

- three, four, and five injection viscosupplements
- topical analgesics, and
- oral analgesics.

3.3.1 Improvement from Baseline

Table 6 provides examples of pharmaceutical agents indicated for the relief of pain for which a clinical study utilized the WOMAC A to assess pain relief from baseline. Of these products, the WOMAC A percent improvement from baseline was as low as 17.2% and as high as 42.9%. The percent improvement observed for Synvisc-One compares favorably to these treatments at 35.8%.

Table 6: Pharmaceutical Products for OA Pain Relief—WOMAC A

Type	Product	Reference	WOMAC A Percent Improvement from Baseline
Systemic Effect/ Frequent Dosing	Celecoxib	Bingham et al. 2007, Birbara et al. 2006, Gibofsky et al. 2003, Lehmann et al. 2005, McKenna et al. 2001, Rother et al. 2007	33.3% to 42.7%
	Diclofenac	Case et al. 2003, McKenna et al. 2001, Schnitzer et al. 2004	27% to 40.2%
	Morphine sulfate ER	Caldwell et al. 2002	17.2%
	Tramadol/acetaminophen	Emkey et al. 2004	29.6%
Local Effect/ Frequent Dosing (2-3 times/day)	Diclofenac topical	Bookman et al. 2004, Grace et al. 1999	36.9% to 42.9%
Local Effect/ Single Injection	Synvisc-One	sPMA (P940015/S012)	35.8%

Table 7 provides examples of other viscosupplement products indicated for the relief of pain for which WOMAC A was used to assess pain relief from baseline.

Viscosupplements including Synvisc-One are comparable to pharmaceutical agents in terms of improvement from baseline.

Table 7: Viscosupplement Products for Pain Relief—WOMAC A

# Injections	Product*	Reference	WOMAC A Percent Improvement from Baseline
5 Injections	Supartz®	Day et al. 2004	42%
4 Injections	Orthovisc®	Brandt et al. 2001	30%
3 to 5 Injections	Euflexxa®	Kirchner and Marshall 2006	30%
1 Injection	Synvisc-One	sPMA (P940015/S012)	35.8%

* The pivotal studies for Synvisc (3 injections) and Hyalgan did not use WOMAC as an outcome measure and therefore are not included in this table.

3.3.2 Effect Size

Effect size is a unitless measurement which enables comparison among clinical trials. Table 8 provides the effect size calculated from several clinical studies on celecoxib and the effect size calculated from the present Synvisc-One study at the end of the trial. Calculated in the same fashion (treatment difference divided by control group standard deviation at the relevant timepoint), the effect size for Synvisc-One for WOMAC A at 26 weeks is 0.22, within the range of the reported results for celecoxib.

Table 8: WOMAC A Effect Size – Comparison to Celecoxib

Reference	Product	Effect Size (Neg. value favors treatment)
Bensen et al. 1999*	celecoxib	-0.50
Zhao 1999*	celecoxib	-0.33
Clegg 2006**	celecoxib	-0.14
Bingham et al. 2007	celecoxib	-0.46
Genzyme sPMA (P940015/S012) 2007	Synvisc-One	-0.22

*Data points taken from Deeks, Smith and Bradley 2002 review

** Also referred to as the “GAIT” study, a large NIH-sponsored study of glucosamine, chondroitin, celecoxib, and placebo.

The effect size observed for Synvisc-One is comparable to those observed for classes of other FDA-approved pharmaceutical products and medical devices indicated for treatment of pain. Compared with pharmaceuticals, which have a systemic effect, or products that require multiple injections, Synvisc-One has the advantage of being a local treatment requiring only one injection. Based on the similar effect sizes, Synvisc-One provides a similar clinical benefit compared to other products currently approved and used in practice to treat OA pain.

Commonly used treatments for knee OA include acetaminophen, NSAIDs, COX-2 inhibitors, intra-articular corticosteroids and intra-articular hyaluronic acid. Published effect sizes for these classes of products range from 0.13 to -0.72. (Bjordal et al., 2004;

Lo et al., 2003; Zhang et al., 2004; Bellamy et al., 2005; Lee et al., 2005; Arrich et al., 2005; Toweed et al., 2006) The effect size of Synvisc-One (-0.22) is well within this range for currently approved products for OA pain.

In general, the differences observed between treatment groups for many currently approved and effective products to treat OA pain would not meet DGRND's threshold of a 10-20 mm difference between groups. (Bjordahl et al., 2007) In fact, in a more recent example, a product approved by CDER in late 2007 for treatment of OA pain (Voltaren® Gel) showed a 7 mm difference in the primary endpoint (WOMAC A [pain]) between the active and control groups (Summary Basis of Approval).

In summary, the response observed with Synvisc-One is within the ranges reported for the treatment effect and effect size for NSAIDs (including celecoxib), acetaminophen and other viscosupplements. The response also exceeds the minimum clinically important improvement as defined by the literature on OA pain. As such, the clinical meaning of the Synvisc-One results has been shown to be commensurate with currently available FDA-approved, and clinically recommended, products for the treatment of pain due to OA.

4. PRODUCT HISTORY AND DEVELOPMENT: SYNVISC-ONE

4.1 Product Description

The material of Synvisc and Synvisc-One is the identical hylan G-F 20, which is either supplied in a 2.25-mL glass syringe (Synvisc) or a 10-mL glass syringe (Synvisc-One). Synvisc is currently approved in the U.S. and over 70 countries worldwide, and has been on the market for more than 10 years. The manufacturing process for hylan G-F 20 material remains unchanged. Synvisc-One combines the three 2 mL Synvisc injections into a single 6 mL injection. In order to accommodate the larger volume of hylan G F 20, the syringe barrel size has been increased from 2.25 mL to 10 mL.

Hylan G-F 20 is a sterile, non-pyrogenic product containing hylan polysaccharide hydrated in physiological saline. It 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 constitutes 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 Daltons).

Hylan B is produced by chemically cross-linking hylan molecules with vinyl sulfone to form an infinite molecular network (Balazs, 1986, US Patent #4,605,691; Balazs, 1993, *Biotechnological Polymers*; Balazs, 1988, *Biotech USA*; Larsen, 1993, *Biomed Mater*).

One milliliter of Synvisc-One contains 8 mg hylan polymer. The hydration fluid is isotonic physiological sodium chloride solution (**Table 9**).

Table 9: Synvisc-One Syringe Contents

Contents	(per mL)
Hylan Polymer	8 mg
Sodium chloride	8.5 mg
Disodium hydrogen phosphate	0.16 mg
Sodium dihydrogen phosphate monohydrate	0.04 mg
Water for Injection (USP)	1.0 mL

4.2 Pre-clinical Development

Safety testing for Synvisc (hylan G-F 20) was originally conducted under tripartite biocompatibility guidance for medical devices. This guidance was superseded by ISO 10993 guidance. Safety testing was updated in compliance with ISO 10993 and was found satisfactory.

The clearance of Synvisc and its gel and fluid components from the rabbit knee joint were determined and reported in the original Synvisc PMA (P940015). The test animals for these studies were New Zealand White rabbits. The radioactive material was administered as a single IA injection of 0.3 mL. On a body weight basis, the test article was administered at a dose of 0.086 mL/kg. This is the same dose level expected to be delivered from a single 6-mL administration of Synvisc-One to a 70-kg human.

All non-clinical and animal testing was conducted on Synvisc, is applicable to Synvisc One and deemed satisfactory. All of these tests were previously conducted on the final product and were found to meet the requirements of the tests. The final reports for these tests are included in the original Synvisc PMA, approved August 8, 1997.

4.3 The Safety and Effectiveness of Synvisc

The safety and effectiveness of the current Synvisc treatment regimen of 2mL as three weekly injections has been extensively studied. Many of these trials have provided Level I evidence (randomized, controlled) of the performance in comparison to various comparators.

A recent evaluation of Synvisc (3 injections) which includes the 6 trials that were part of the original PMA along with 18 other trials (and many other products in the viscosupplement class) is available through an independent meta-analysis (Cochrane, et al, 2006 (Oxford). The specific analyses of Synvisc alongside various other comparators are presented in detail in this published review, and therefore not provided in this summary. The Synvisc Package Insert also contains a summary of safety and effectiveness data (Included in Panel Package).

4.4 Development of a Single-dose Regimen

Synvisc 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. Currently, the recommended treatment regimen for the treatment of knee OA pain is three 2-mL IA injections, given weekly. In order to investigate reducing the number of IA injections for the convenience of patients and physicians, a pilot study was conducted. The data indicated that at 6 months post-injection, a 1 x 6 mL treatment regimen had a similar efficacy and safety profile as the 3 x 2 mL regimen (Conrozier, 2008, *Arch Orthop Trauma Surg*). Therefore, pivotal study SYN00704 was designed to test the efficacy and safety of 1 x 6 mL hylan G-F 20 against a control consisting of arthrocentesis and IA injection of saline.

4.5 Regulatory history

Synvisc was originally marketed in the European Union in 1995 and was approved in the USA (P940015) on August 8, 1997. Currently, it is marketed in over 70 countries worldwide.

Currently, there is no single-injection hyaluronic acid (HA) viscosupplementation product available for use in OA in the USA. Synvisc-One has recently been approved for use in the European Union.

All Synvisc-One–related clinical studies were conducted in accordance with Good Clinical Practices (GCP) and local laws and regulations. Clinical trial applications were submitted to appropriate competent authorities within each country where clinical sites were located, appropriate ethics committee reviews were held for each clinical site or region involved in a clinical trial, and written informed consent was received from each patient enrolled in a clinical study.

Prior to submission of the PMA Supplement, a pre-submission advice meeting was held between FDA and Genzyme on May 21, 2007. The protocols, statistical analyses and results were presented to FDA. FDA provided guidance on the information needed to assess the foreign study acceptability, as well as general advice and requests for the PMA Supplement. FDA’s guidance and requests were incorporated into the PMA Supplement

submitted on June 18, 2007. An Investigational Device Exemption (IDE) was not submitted to FDA for any of these studies as there were no clinical sites within the USA.

Subsequent to the review, Genzyme received a deficiency letter from the Agency on October 31, 2007, requesting additional information concerning the “clinical meaning” of the study results, analysis of the secondary endpoints, and quality system/manufacturing-related documents. Genzyme requested a second meeting with DGRND to discuss these issues for the reasons discussed so far in this summary document. No consensus was reached during this meeting on April 29, 2008.

Following the meeting on April 29, 2008, a response was submitted by Genzyme addressing each of the deficiencies outlined in the October 31, 2007 letter. As part of this response, Genzyme requested, and FDA granted, an FDA advisory panel to help resolve the open issue with regard to determining the appropriate threshold for clinical meaning for the Synvisc-One clinical trial results.

5. FDA-REQUESTED RE-ANALYSES

During review of the supplement, FDA requested that Genzyme perform re-analyses of the data. These analyses included re-analyses of the WOMAC A (primary endpoint) and WOMAC C using a mixed effects model (repeated measures ANCOVA) with site as a random effect in place of the pre-specified model with site as a fixed effect.

These analyses were supportive of the pre-specified analyses.

6. RISK-BENEFIT EVALUATION

The proposed alternate treatment regimen for Synvisc-One combines the three injections (2 mL each) of Synvisc into one injection of 6 mL. The composition of the device (hylan G-F 20) has not changed. This product is currently approved in the USA and numerous countries worldwide, and has been on the market for more than 10 years. Millions of patients have received an intra-articular injection of Synvisc, and the global post-market surveillance indicates that the reporting rate of adverse effects is low. The events are typically limited to the injected joint (pain, swelling, effusion) and manageable. With Synvisc-One, a patient would receive a single 6 mL injection given during one office visit instead of one (2 mL) injection given at each of three office visits for a total of 6 mL.

The potential risks introduced with the alternate treatment regimen include:

- Possible change in AE profile due to the larger volume of hylan G F 20 being injected into the joint space
- Possible safety concerns associated with increasing the minimum recommended needle size from 22 gauge to 20 gauge to allow for ease of extrusion of the product from the syringe

The clinical trial of Synvisc-One specifically demonstrated an overall safety profile consistent with that of the current 3-injection regimen during both the initial and repeat phases. Therefore, the two potential new risks described above were not observed.

The potential benefits associated with the alternate treatment regimen can be considered from the perspectives of the patient with knee OA and the U.S. healthcare system.

The benefits to patients include:

- Improvement from baseline in OA pain and self assessed health condition
- Analgesic effect similar to other approved therapies for OA and chronic pain, but with less risk of systemic toxicity

- Compared with current 3-5–injection regimens of viscosupplements, a single-injection regimen offers 100% compliance, thus ensuring that the patient receives optimal benefit from therapy
- The safety and convenience of a single intra-articular injection into the knee versus 3-5 injections required for currently approved viscosupplements
 - Decreased risk because of fewer injections
 - Less time spent away from work or other important activities due to simplified treatment

The benefits to the healthcare system of approval of Synvisc-One include:

- Reduced costs due to 2-4 fewer office visits
- Reduced costs due to 2-4 fewer arthrocentesis procedures,

Genzyme therefore believes that the overall risk/benefit is favorable and the simplified treatment regimen of Synvisc provides additional benefits to patients and health care providers alike.

7. CONCLUSION

- Synvisc-One is a simplified treatment regimen of Synvisc which has been marketed for over 10 years world wide. Millions of patients have received an intra-articular injection of Synvisc, and the global post-market surveillance indicates that the reporting rate of adverse effects is low.
- There is an unmet medical need to simplify treatment.
- The Pivotal trial showed that Synvisc-One provides relief from OA pain as evidenced by the totality of the data obtained using validated outcomes measures:
- The primary endpoint measuring OA-related pain for the duration of the trial was met
- All secondary endpoints trended in favor of Synvisc-One, many of which reached statistical significance
- The initial and repeat safety profile was commensurate with the three dose regimen of Synvisc
- The trial data indicates that the superior outcome obtained in the Synvisc-One treatment group is clinically meaningful
- The improvement from baseline exceeds minimum clinically important improvement (MCII) as defined in the literature
- Patients, who were unaware of treatment assignment, were twice as likely to rate themselves as feeling better after Synvisc-One treatment. This observation was corroborated by the blinded clinical observer assessment.
- Both the observed improvement and treatment effect are consistent with many other approved OA therapies.
- Considering the success of the pivotal trial for Synvisc-One, viewed within the context of currently approved products for OA, and published medical literature, this alternate treatment regimen is approvable.

8. REFERENCES

Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. *Arthritis Rheum.* 1986; 29(8):1039-1049.

Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. *Arthritis Rheum.* 2001; 45(4):384-391.

Angst, F., Aeschlimann, A., Michel, B.A., et al. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. *J. Rheumatol.* 2002; 29(1):131-138.

Arnold LM, Russell, I.J., Duan, W.R., et al. Pregabalin for management of fibromyalgia syndrome (FMS): a 14-week, randomized, double-blind, placebo-controlled, monotherapy trial. 2007; *Presented at the 59th Annual Scientific Meeting of the American Academy of Neurology* (Boston, MA).

Arrich J, Piribauer F, Mad P, et al. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. *Can Med Assoc J* 2005; 172(8):1039-1043.

Balazs 1986 US Patent 4,605,691

Balazs EA, Leschiner E, Larsen NE, et al. Applications of hyaluronan and its derivatives. In: Gebelein CG, eds. *Biotechnological Polymers*. Lancaster, PA: Technomic Publishing Co. Inc., 1993.

Balazs 1988 Biotech USA

Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to anti-rheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol.* 1988; 15(12):1833-1840.

Bellamy, N., Carr, A., Dougados, M., et al. Towards a definition of “difference” in osteoarthritis. *J. Rheumatol.* 2001; 28(2):427-430.

Bellamy N, Campbell J, Robinson V, et al. Intra-articular corticosteroid for treatment of osteoarthritis of the knee. *The Cochrane Libr (Oxford)* 2006;(2):ID #CD005328.

Bensen, W., Fiechtner, J., McMillen, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999; 74: 1095.

Bingham, C.O., 3rd, Sebba, A.I., Rubin, B.R., et al. Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. *Rheumatol.* 2007; 46(3):496-507.

Birbara, C., Ruoff, G., Sheldon, E., et al. Efficacy and safety of rofecoxib 12.5 mg and celecoxib 200 mg in two similarly designed osteoarthritis studies. *Curr. Med. Res. Opin.* 2006; 22:199-210.

Bjordal JM, Klovning A, Ljunggren AE, et al. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomized placebo-controlled trials. *Eur J Pain.* 2007;11:125-138.

Bjordal JM, Ljunggren AE, Klovning et al. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ* 2004; 329:1317-1322.

Bookman, A.A.M., Williams, K.S.A., Shainhouse, J.Z. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. *Can. Med. Assoc. J.* 2004; 171(4):333-338.

Brandt KD, Block JA, Michalski JP, et al., and the Orthovisc® Study Group. Efficacy and safety of intra-articular sodium hyaluronate in knee osteoarthritis. *Clin. Orthop.* 2001; 385:130-143.

Caldwell J.R., Rapoport, R.J., Davis J.C., et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J. Pain Symptom Manage.* 2002; 23(4):278-291.

Case, J.P., Baliunas, A.J., Block, J.A. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. *Arch. Intern. Med.* 2003; 163(2):169-178.

Clegg, D.O., Reda, D.J., Harris, C.L., et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *New Engl. J. Med.* 2006; 354(8):795-808.

Conrozier T, Jerosch J, Beks P, et al. Prospective, multi-centre, randomised evaluation of the safety and efficacy of five dosing regimens of viscosupplementation with hylan G-F 20 in patients with symptomatic tibio-femoral osteoarthritis: a pilot study. *Arch Orthop Trauma Surg.* In press 2008, 10.1007/s00402-008-0601-2.

Copay, A.G., Subach, B.R., Glassman, S.D., et al. Understanding the minimum clinically important difference: a review of concepts and methods. *Spine J.* 2007; 7(5):541-546.

Day, R., Brooks, P., Conaghan, P.G., et al. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intra-articular hyaluronan in osteoarthritis of the knee. *J. Rheumatol.* 2004; 31:775-782.

Dickson DJ, Hosie G, English JR, et al. A double-blind, placebo-controlled comparison of hylan G-F 20 against diclofenac in knee osteoarthritis. *J. Clin. Res.* 2001; 4:41-52.

Dworkin, R.H., Turk, D.C., Wyrwich, K.W., et al. Consensus Statement—Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *J. Pain* 2008; 9(2):105-121.

Emkey, R., Rosenthal, N., Wu, S.C., et al. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet®) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal anti-inflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. *J. Rheumatol.* 2004; 31(1):150-156.

Farrar, J.T., Young, J.P., Jr., LaMoreaux, L., et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94(2):149-158.

Gibofsky, A., Williams, G.W., McKenna, F., et al. Comparing the efficacy of cyclooxygenase 2-specific inhibitors in treating osteoarthritis: appropriate trial design

considerations and results of a randomized, placebo-controlled trial. *Arthritis Rheum.* 2003; 48(11):3102-3111.

Grace, D., Rogers, J., Skeith, K. et al. Topical diclofenac versus placebo: a double blind, randomized clinical trial in patients with osteoarthritis of the knee. *J. Rheumatol.* 1999; 26(12):2659-2663.

Kellgren JH, Lawrence JS. Radiographic assessment of osteoarthritis. *Ann Rheum Dis.* 1957; 16:494-502.

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):1261-1269.

Kirchner, M., Marshall, D. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage* 2006; 14:154-162.

Kvien, T.K., Heiberg, T., Hagen, K.B. Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): What do these concepts mean? *Ann. Rheum. Dis.* 2007; 66(Suppl. 3):iii40-iii41.

Larsen NE, Pollack CT, Reiner K, et al. Hylan gel biomaterial: dermal and immunologic compatibility. *Journal of Biomedical Materials Research.* 1993; 27:1129-34.

Lee C, Hunsche E, Balshaw R, et al. Need for common internal controls when assessing the relative efficacy of pharmacologic agents using a meta-analytic approach: case study of cyclooxygenase 2-selective inhibitors for the treatment of osteoarthritis. *Arthritis Care Res* 2005; 53:510-518.

Lehmann, R., Brzosko, M., Kopsa, P., et al. Efficacy and tolerability of lumiracoxib 100 mg once daily in knee osteoarthritis: a 13-week, randomized, double-blind study vs. placebo and celecoxib. *Curr. Med. Res. Opin.* 2005; 21(4):517-526.

Lo GH, LaValley M, McAlindon T, et al. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003; 290:3115-3121.

McKenna, F., Borenstein, D., Wendt, H., et al. Celecoxib versus diclofenac in the management of osteoarthritis of the knee. *Scand. J. Rheumatol.* 2001; 30:11-18.

Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage.* 2004; 12(5):389-399.

Raman R, Dutta A, Day N, et al. Efficacy of hylan G-F 20 and sodium hyaluronate in the treatment of osteoarthritis of the knee — a prospective, randomized clinical trial. *Knee* 2008; 15(4):318-324

Raynauld JP, Torrance GW, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results. *Osteoarthritis Cartilage.* 2002;10(7):506-517.

Rother, M., Lavins, BJ., Kneer, W., et al. Efficacy and safety of epicutaneous ketoprofen in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: multicentre randomised controlled trial. *Ann. Rheum. Dis.* 2007; 66:1178-1183.

Salaffi, F., Stancati, A., Silvestri, C.A., et al. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. 2004; *Eur. J. Pain.* 8(4):283-291.

Schnitzer, T.J., Beier, J., Geusens, P. et al. Efficacy and safety of four doses of lumiracoxib versus diclofenac in patients with knee or hip primary osteoarthritis: a phase II, four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2004; 51(4):549-557.

Synvisc (hylan G-F 20) Package Insert. Ridgefield, NJ: Genzyme Corporation; 2006.

Toweed TE, Maxwell L, Judd MG, et al. Acetaminophen for osteoarthritis. *Cochrane Database Syst. Rev.* 2006; (1):CD004257.

Tubach F., Ravaud, P., Baron, G., et al. (originally published online 18 June 2004; doi:10.1136/ard.2004.022905). Evaluation of clinically relevant changes in patient

reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann. Rheum. Dis.* 2004; 2005; 64:29-33.

Tubach, F., Wells, G.A., Ravaud, P. et al. Minimal clinically important difference, low disease activity state, and patient acceptable symptom state: methodological issues. *J. Rheumatol.* 2005; 32(10):2025-2029.

Tubach, F., Ravaud, P., Beaton, D. et al. Minimal clinically important improvement and patient acceptable symptoms state for subjective outcome measures in rheumatic disorders. *J. Rheumatol.* 2007; 34(5):1188-1193.

Wobig M, Dickhut A, Maier R, et al. Viscosupplementation with hylan G-F 20 : a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin. Ther.* 1998; 20(3):410-423.

Zhang W, Robertson J, Jones AC, et al. The placebo effect and its determinants in osteoarthritis meta-analysis of randomized controlled trials. *Ann Rheum Dis.* 2008;10.1136/ard.2008.092015.

Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2004; 63:901-907.