University of California, San Francisco UCSF-SYNVISC-ONE 001 NCT01625013

GENZYME SYNVISC-ONE

Clinical Research Protocol

LONG-TERM MANAGEMENT OF "YOUNGER, ACTIVE" PATIENTS WITH PAIN FROM EARLY KNEE OSTEOARTHRITIS WITH SYNVISC-ONE (HYLAN G-F 20)

Protocol Number:	UCSF-SYNVISC-1 Version 001
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IDE Number:	Pending
Development Phase:	Phase III
Sponsor:	Anthony Luke, MD, MPH 1500 Owens St, San Francisco, CA, 94158
Funding Organization:	Genzyme
Principal Investigator:	Name: Anthony Luke, MD, MPH Telephone: 415-885-3807 Fax: 415-885-3838 E-mail:lukea@orthosurg.ucsf.edu
Medical Monitor:	Name: Anthony Luke, MD, MPH Telephone: 415-885-3807 Fax: 415-885-3838 E-mail:lukea@orthosurg.ucsf.edu
Coordinating Center:	Single Site

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LIST OF ABBREVIATIONS

AE	Adverse event
CFR	Code of Federal Regulations
CRF	Case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PI	Principal Investigator
SAE	Serious adverse experience
NSAID	Non-steroidal anti-inflammatory drugs: also known as "NSAIDs"; medication used to treat pain or swelling.
OA	Osteoarthritis

PROTOCOL SYNOPSIS

TITLE	Long-term Management of "Younger, Active" Patients with Pain from Early Knee Osteoarthritis with Synvisc-One (hylan G-F 20)
SPONSOR	Dr. Anthony Luke, University of California San Francisco
FUNDING ORGANIZATION	Genzyme
NUMBER OF SITES	1
RATIONALE	The objectives of the study are to assess the effectiveness, duration of symptom relief, improvements on activity level and safety of one or more hylan G-F 20 injections for symptomatic early knee osteoarthritis (OA) treatment in younger, active patients over a three-year period. •From a pain management perspective, reduction of knee pain knee pain will target a Patient Acceptable Symptom State (PASS) •Repeated hylan G-F 20 treatment will be allowed as necessary to maintain patients in PASS throughout the duration of the study period.
STUDY DESIGN	Typically viscosupplementation is considered an intervention for knee osteoarthritis in older patients who are less active. Many young active patients can also develop knee osteoarthritis after trauma or surgery or for congenital reasons. Treatment of these patients commonly are steroid injections which have more biologically detrimental effects for cartilage compared to viscosupplementation. This study aims to study use of viscosupplementation for young individuals who are active. Synvisc One injections, which are a single injection, will be used to determine effectiveness of reducing pain and maintaining an active healthy lifestyle for younger patients aged 30-50 years old. This study, for research purposes only, will be an open label longitudinal cohort study with natural history over 3 years. Subjects

	enrolled in the cohort will have baseline functional testing performed including a motion gait analysis, 12 minute walk test, and 3-day accelerometer data. Subjects will receive a single 6 mL intra-articular injection of hylan G-F 20 in the target knee at baseline. All ongoing treatments will be monitored at 6-month intervals over the 3-year duration of the study. Patients can receive any other conservative treatments (e.g., oral medications, physical or other therapy, acupuncture, etc., except other injection treatments) and current treatments will be documented during each patient encounter. An initial injection of hylan G-F 20 will be injected in the symptomatic knee using a standard supine lateral approach using a 20-gauge needle. A face-to-face follow up visit will be carried out 6 months after first injection with additional face to face meetings every 6 months thereafter unless the subject requires an additional injection of hylan G-F 20. Hylan G-F 20 treatments can be administered up to three times each year during the study duration. After each injection, follow up measures will be carried out using secure e-mail or phone contact at 6 weeks, 12 weeks, 18 weeks after each in-office evaluation or injection. Follow up will consist of WOMAC, Lysholm score, and Tegner score. Patients may return for retreatment of hylan G-F 20 if symptoms recur after at least 4 months following their previous injection and they meet the inclusion criteria for pain levels on the following WOMAC questions A1 (How much pain have you had walking on a flat surface?), C8 (How much difficulty have you had going down the stairs?), C9 (How much difficulty have you had when going up the stairs?), C10 (How much difficulty have you had when getting up from a sitting position?) and/or C23 (How much difficulty have you had while doing heavy household chores?). Inclusion criteria for pain level is defined by selecting moderate, severe, or extreme on all questions A1, C8, C9, C10 and/or C23. Those subjects who select mild or no pain levels on any of A1, C8, C9, C10 and/or C23, will not meet the criteria for WOMAC pain level and retreatment. Patients requiring three injections of hylan G-F 20 in 4 months or less will be allowed to exit the cohort after their six-month follow up following the third injection. Otherwise, patients will be followed until they reach the 3-year follow up, or drop out for other injection treatments or surgical treatment. Therefore, patients would potentially be able to receive up to 9 injections during the 3-year study.
PRIMARY OBJECTIVES	Specific Aim 1: To identify whether injection of 6 mL hylan G-F 20 decreases pain over 26 weeks in young (ages 30 to 50 years) active patients with symptomatic primary osteoarthritis of the knee not treated previously with hylan G-F 20.

SECONDARY OBJECTIVES	Specific Aim 2: Though symptoms can be improved for periods up to 6 months, pain symptoms can recur. The effect of repeated treatments of hylan G-F 20 will be studied. Specific Aim 3: To identify the effects of treatment with hylan G-F 20 on activity levels (using objective activity measures utilizing accelerometer and Physical Activity Enjoyment Scale (PACES) and quality of life scores (WOMAC, SF-12) comparing baseline to treatment at 3 months. Specific Aim 4: To understand the natural history of conservative treatment on this cohort of patients over a 3 year period.
NUMBER OF SUBJECTS	150
SUBJECT SELECTION CRITERIA	<u>Inclusion Criteria</u>: Male or female patients aged 30-50 years History of symptomatic unilateral primary or secondary knee OA for more than 6 months Signed written informed consent Radiographic evidence of Kellgren-Lawrence Grade I or II OA of the target knee Body Mass Index (BMI) < 30 kg/m2 Activity criteria (Tegner score > 3) Continued target knee OA pain despite conservative treatment ≥ 3 months (e.g., weight reduction, physical therapy, analgesics) Willing to withhold intake of NSAIDs (including COX-2 inhibitors) and analgesics, for a washout period of minimum 3 days up to 21 days prior to baseline visit (depending on medication) Willing to discontinue prohibited treatments and medications throughout study period Baseline inclusion criteria • Completed OA medication washout period • Target knee pain 4-8 (0-10 NRS) during most painful knee movement (Worst Knee Pain) • If female, must have had a negative urine pregnancy test and

	used a medically acceptable form of contraception for at least 1 month prior to baseline and agree to continued use of contraception for the duration of the study. Otherwise, females must be surgically sterile, or postmenopausal (as documented in medical history) for at least 1 year. The fetal safety profile for G-F 20 is unknown. Pregnancy will affect the individual's regular activity levels. Females who become pregnant during the study will be excluded from the study. Subjects who become pregnant will be followed up by telephone every 3 months to check for any adverse effects. They willl also be recommended to follow routine obstetric visits. Males should be able to father children as it has no expected effects on activty levels. Exclusion Criteria: Known allergy to hylan G-F 20 or any of its components, or to avian proteins, eggs, feathers, down, or poultry Clinically apparent tense effusion or other acute inflammation of the target knee at baseline History of target knee viscosupplementation treatment History of major surgery for OA in target knee including arthroplasty or tibial osteotomy Arthroscopic surgery or intraarticular steroid injection in target knee within six months of baseline visit Significant (as judged by the Investigator) alignment deformity of target knee Ipsilateral symptomatic OA of hip or ankle; contralateral symptomatic OA of hip, knee, or ankle History of: Septic OA of any joint Inflammatory arthropathy such as RA, gout, pseudogout, lupus, crystaline in-flammatory arthopathy Active infection of lower extremity Known significant acute and/or concurrent medical disease including, but not limited to current malignancy, history of transplant surgery, congestive heart failure, significant unstable cardiovascular disease, renal hepatic pulmonary, endocrine, metabolic, or GI condition Any known contraindication to acetaminophen Venous or lymphatic stasis in either leg Peripheral vascular disease Patient has been prescribed chronic opioid analgesics at time of baseline visit Concurrent multi-system or multi-limb trauma Patient plans to become pregnant during study period

	Patient plans to move significantly out of area, have surgery, or initiate or cease other OA treatments Knee pain improves during washout period Workman's Comp patient
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Synvisc G-F 20 will be injected in the symptomatic knee using a standard supine lateral approach using a 20-gauge needle. Patients will be treated at baseline and followed out to three years. Patients may return for retreatment as early as 4 months post their prior injection if they meet the retreatment criteria pain levels for Worst Knee Pain. If the subjects need another injection, the follow-up cycle will restart at Visit 1 and the subject will be seen every 6 months and followed-up for 3 years.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	N/A

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Patients may return for retreatment as early as 4 months post their prior injection if they meet the retreatment criteria pain levels for Worst Knee Pain. If the subjects need another injection, the follow-up cycle will restart at Visit 1 and the subject will be seen every 6 months and followed-up for 3 years. Approximate Time Requirements: • Baseline Screening: Informed Consent, Physical exam, patient questionnaire, injection, X-ray, walk test (Approx. 2 hours) and accelerometer test (3 days) • 6 months after injection: Physical exam, patient questionnaire, walk test (Approx. 1 hr) and accelerometer test (3 days) • 12 months after injection: Physical exam, patient questionnaire, walk test (Approx. 1 hr) and accelerometer test (3 days) • 18 months after injection: Physical exam, patient questionnaire, walk test (Approx. 1 hr) and accelerometer test (3 days) • 24 months after injection: Physical exam, patient questionnaire, walk test (Approx. 1 hr) and accelerometer test (3 days) • 30 months after injection: Physical exam, patient questionnaire, walk test (Approx. 1 hr) and accelerometer test (3 days) • 36 months after injection: Physical exam, patient questionnaire, walk test (Approx. 1 hr) and accelerometer test (3 days) • 15 min email or phone contact at 6, 12, and 18 weeks post each injection and clinic visit (total 4.5 hrs) Total time for the study will be approximately 8 clinical hours over 3 years, 21 days for the accelerometer test and 4.5 hrs of email/phone contact.
CONCOMMITANT MEDICATIONS	Allowed: Patients can receive any other conservative treatments (e.g., oral medications, physical or other therapy, acupuncture, etc., except other injection treatments) and current treatments will be documented during each patient encounter. Prohibited: Since Synvisc is an elastoviscous fluid device injected directly into the knee joint, it does not interfere with any medicine that your physician recommends, including pain relievers and anti-inflammatory drugs.
EFFICACY EVALUATIONS	Efficacy will be measured and evaluated using data from the following assessments: KOOS, Lysholm, SF-12, WOMAC, and Accelerometer ™.

PRIMARY ENDPOINT	The primary endpoint for the study will be analyzed using a responder analysis. The proportion of responders following injection within the 6 months following the baseline injection will be calculated based on Worst Knee Pain scores ≤ 3 on a 0-10 pain scale, which is a threshold consistent with other similar studies (Tubach 2005, Bellamy 2010). The primary endpoint is defined as non-inferiority of the proportion of responders in our study relative to an external criterion for the responder proportion (Bellamy 2010).
SECONDARY ENDPOINTS	Survival analysis statistics will be performed to assess duration of benefit from the hylan G-F 20 injections over time. A specific timeframe of interest will be the initial 6 months of treatment following the second and any subsequent hylan G-F 20 injection. Changes from baseline to three months post-treatment in activity levels (using objective activity measures utilizing accelerometer and Physical Activity Enjoyment Scale) and quality of life scores (WOMAC, SF-12) will be determined. We will examine the time courses of longitudinal measures of pain score, activity level, and quality of life over the entire three-year span of the study.
SAFETY EVALUATIONS	The repeat treatment phase evaluated the safety profile of a second injection of Synvisc-One. One hundred and sixty patients were treated during this phase of the study, of which 77 patients received a second injection of Synvisc-One. These patients were followed for 4 weeks and out of 77 patients, only 4 (5.2%) experienced device-related AEs in the injected knee. All such events were mild to moderate and were treated symptomatically. Patients who developed injected knee AEs during the initial phase of the study, and who subsequently received repeat treatment, did not experience injected knee AEs upon repeat exposure to Synvisc-One.
PLANNED INTERIM ANALYSES	There is no interim analysis planned. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

STATISTICS **Primary Analysis Endpoint**	The primary endpoint for the study will be analyzed using a responder analysis. The proportion of responders following injection within the 6 months following the baseline injection will be calculated based on Worst Knee Pain scores ≤ 3 on a 0-10 pain scale, which is a threshold consistent with other similar studies (Tubach 2005, Bellamy 2010). The primary endpoint is defined as non-inferiority of the proportion of responders in our study relative to an external criterion for the responder proportion (Bellamy 2010). Bellamy demonstrated in his paper from 2007 (table 3) that a BLISS response at any time during the study was achieved in 70% receiving appropriate care and Hylan G-F 20 and only in 38% of patients receiving appropriate care (P<0.0001). We propose a non-inferiority delta of 20% relative to this external criterion, and thus the primary endpoint will be tested by a test of our sample proportion (p) with null hypothesis H0: p<0.50 vs. alternative hypothesis H1: p≥0.50. This test will be performed using the Wilson-Agresti method for testing a single binomial proportion at a one-sided significance level of 0.025 (i.e. non-inferiority will be satisfied if the 95% Wilson-Agresti (REF BROWN ET AL 2001) interval for the proportion of responders excludes the null rate of 0.50).
STATISICS **Secondary Endpoints**	For subsequent injections, duration of response over time and median duration of response will be estimated using survival analysis techniques. Inference for activity levels and quality of life will focus on changes from baseline to 3 months. We will examine the time course for the longitudinal data on pain score, activity level, and quality of life measures across the three years of the study using mixed effects models.
Rationale for Number of Subjects	Power Calculation Bellamy demonstrated in his paper from 2007 (table 3) that a BLISS response at any time during the study was achieved in 70% receiving appropriate care and Hylan G-F 20 and only in 38% of patients receiving appropriate care (P<0.0001). A power calculation using a one-sample comparison of proportion with hypothesized value sample size was performed to determine non-inferiority to the 70% results quoted by Bellamy. Power calculations were measured using STATA's SAMPSI calculator. If we postulate a 20% non-inferiority limit (i.e. that at least 50% of patients receiving G-F 20 will achieve a BLISS response), the sample size required to have 90% power and

	$\propto$=0.025 to show non-inferiority at 50% would be 70. For a 10% non-inferiority limit with 90% power and $\propto$=0.025, the required sample size is 274, and for 15% non-inferiority limit with 90% power and $\propto$=0.025, it is 124 patients. These numbers do not allow for dropouts, therefore, we intend to recruit 150 subjects to account for dropout. Conservatively assuming a 20% rate of drop-out, the resulting sample size of n=120 has better than 90% power (one sided test with $\propto$=0.025) to show non-inferiority assuming the true responder rate is 65% (i.e. not quite as high as the 70% external reference).
DATA MANAGEMENT PLAN	Data management and analysis for the study will be performed by the Biostatistics Consulting Unit (BCU) of UCSF's Clinical and Translational Science Institute (CTSI). Data will be stored on a HIPAA-compliant server. The server room has state-of-the-art environmental controls and security features and is protected by a firewall and anti-virus software.

1 BACKGROUND

Treatment of younger patients between 30-50 years of age with knee osteoarthritis is a challenging treatment problem for physicians. The younger, active population has different expectations for management of osteoarthritis with a strong desire to maintain their physical activities and quality of life. Ideally, treatments for osteoarthritis in these patients that can allow them to maintain their activity levels and provide clear future health benefits of regular exercise are preferred. There is a lack of effective treatment for individuals including surgical options with mild osteoarthritis outside of physical therapy exercises, oral analgesic medications, and steroid injections which have possible negative side effects and short durations of symptom improvement. Hylan G-F 20 in a single injection form can provide analgesic benefit up to 6 months and can be used as a treatment in younger patients not improving with traditional treatments.[1]

1.1 Overview of Non-Clinical Studies

Preclinical investigations have demonstrated that Hylan G-F 20 can favorably affect chondrocyte metabolism and recent clinical studies [Ann Rheum Dis. 2004 May; 63(5):478-82; Osteoarthritis Cartilage. 2005 Mar;13(3):216-24] provide support for a disease-modifying effect of Hylan G-F 20 therapy. An evaluation of the non-clinical tests by FDA was based in large part on the previous device approval (for three injections). There were no unresolved safety issues.

1.2 Overview of Clinical Studies

Studies in populations with osteoarthritis of the knee demonstrate that after 3 or more years of follow-up, individuals have worsening of limitations in activities.2 In one study 48.7% of limitations (n= 405) participants with knee symptoms were classified as experiencing a poor two-year outcome using a dichotomous outcome measure of activity.3 Prognostic factors for worsening of limitations in activities include increased pain, reduced ROM, and decreased muscle strength at 1-year follow-up; higher morbidity count; and to a lesser extent poor cognitive functioning. Continuing exercise is important, as there are numerous health benefits for reducing chronic diseases such as hypertension, diabetes and obesity. While osteoarthritis is also a chronic disease, it is focal in nature whereas lack of exercise can result in increased incidence of systemic chronic diseases that have more detrimental health effects and health care costs.5 A single injection preparation of hylan G-F 20 (6 mL) has shown improvement over placebo in a double blind randomized control trial.1 Hylan G-F 20 has demonstrated improvements with repeated treatment of knee osteoarthritis using a series of three 2 mL preparations4; however, the effectiveness of repeated injections of the 6 mL is not yet known. Maintaining activity levels and pain tolerance are important in the younger age group as this translates to continuing good mobility and ability to work.

A randomized, double-blind, saline-controlled, multicenter trial of 253 patients (mean age 63 years) with moderate to severe OA knee pain. Most had radiographically confirmed Kellgren-Lawrence grade II or III OA at baseline. Patients initially received arthrocentesis and then either one 6-mL injection of Synvisc-One or one 6-mL injection of placebo (saline). Follow-up visits occurred at weeks 1, 4, 8, 12, 18, and 26. The primary end point

was the difference between the groups in the change from baseline in patient-assessed pain as measured by the WOMAC A score (average of 5 questions) over 26 weeks. A responder was defined as a patient with a ≥1 category improvement in WOMAC question A1 and no knee-related adverse events. The safety of repeat treatment (week 26) with Synvisc-One was assessed in all patients over a 4-week period. Acetaminophen rescue was permitted up to 48 hours before study visits.

Two medical studies involving a total of 132 patients were done in Germany. The patients in these studies were at least 40 years old and had knee pain due to OA. The patients were placed in one of two groups. One group was given an injection of SYNVISC into one or both knees once a week for three weeks. The second group was given an injection of salt water once a week for three weeks. As part of the study, knee joint pain was measured for 26 weeks. Also, patients and doctors were asked to judge the success of the treatment for 26 weeks. Patients with OA knee pain, who did not get pain relief with other medicines, got pain relief with SYNVISC. The patients given SYNVISC had more pain relief than the patients given salt water. Some patients started to feel pain relief after the first week of SYNVISC treatment. The most pain relief and the greatest amount of treatment success was seen 8 to 12 weeks after SYNVISC treatment started. A medical study done in the United States involved 90 patients. The patients were at least 40 years old and had knee pain due to OA. Patients were placed into one of two groups. One group was given SYNVISC once a week for three weeks. The second group had a needle inserted into the knee to have any fluid removed (this procedure is called arthrocentesis [pronounced AR-thro-sen-TEE-sis]) once a week for three weeks. Patients improved after SYNVISC treatment, but not more than patients who had arthrocentesis. This study was different from the German studies because the last time the two groups were compared was only two weeks after the last SYNVISC injection. The study was also different in other ways, including length of time that patients had to stop taking medicines before they could start treatment. The length of time patients had to stop taking medicines was two weeks in the German studies and, four weeks in the U.S. study.

2 STUDY RATIONALE

There is a lack of effective treatment for individuals including surgical options with mild osteoarthritis outside of physical therapy exercises, oral analgesic medications, and steroid injections which have possible negative side effects and short durations of symptom improvement. Hylan G-F 20 in a single injection form can provide analgesic benefit and can be used as a treatment in younger patients not improving with traditional treatments. This study is for research purposes only.

RISK / BENEFIT ASSESSMENT

Young patients with osteoarthritis are typically not surgical candidates. Randomized control trials for arthroscopy in arthritis patients do not show long term benefits. Patients want conservative treatment with low side effect profiles which can improve their quality of life. Hylan G-F 20 in a single injection form can provide analgesic benefit for patients with knee osteoarthritis. The treatment may reduce the need for oral medications and facilitate rehabilitation exercises. Patients may have better exercise tolerance with less pain. As shown in medical studies of patients with osteoarthritis (OA) of the

knee, where approximately half received a single injection of SYNVISC and the other half either had fluid removed from the knee and/or received injections of the same volume of salt water (a "Saline Control" injection), the major benefits of SYNVISC are pain relief and improvement in other symptoms related to OA of the knee.

STUDY OBJECTIVES

2.1 Primary Objective

There are two primary objectives to this study:

Specific Aim 1: To identify whether injection of 6 mL hylan G-F 20 decreases pain over 26 weeks in young (ages 30 to 50 years) active patients with symptomatic primary osteoarthritis of the knee not treated previously with hylan G-F 20.

Specific Aim 2: Though symptoms can be improved for periods up to 6 months, pain symptoms can recur. The effect of repeated treatments of hylan G-F 20 will be studied.

2.2 Secondary Objectives

There are two secondary objectives to this study:

Specific Aim 3: To identify the effects of treatment with hylan G-F 20 on activity levels (using objective activity measures utilizing accelerometer and Physical Activity Enjoyment Scale (PACES)) and quality of life scores (WOMAC, SF-12) comparing baseline to treatment at 3 months.

Specific Aim 4: is to understand the natural history of conservative treatment on this cohort of patients over a 3 year period.

3 STUDY DESIGN

3.1 Study Overview

This study aims to study use of viscosupplementation as a treatment of pain for young individuals who are active. Typically viscosupplementation is considered an intervention for knee osteoarthritis often for older patients who are less active. Many young active patients can also develop knee osteoarthritis after trauma or surgery or for congenital reasons. Treatment of these patients commonly are steroid injections which have more biologically detrimental effects for cartilage compared to viscosupplementation Synvisc One injections which are a single injection will be used to determine effectiveness of reducing pain and maintaining an active healthy lifestyle for younger patients aged 30-50 years old.

This study will be an open label longitudinal cohort study with natural history over 3 years. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. Subjects enrolled in the cohort will have baseline functional testing performed including a motion gait analysis, 12 minute walk test, and 3-day accelerometer data. Subjects will receive a single 6 mL intra-articular injection of hylan G-F 20 in the target knee at baseline. All ongoing treatments will be monitored at 6 month intervals over the 3 year

duration of the study. Patients can receive any other conservative treatments (e.g., oral medications, physical or other therapy, acupuncture, etc., except other injection treatments) and current treatments will be documented during each patient encounter. An initial injection of hylan G-F 20 will be injected in the symptomatic knee using a standard supine lateral approach using a 20 gauge needle. A face to face follow up visit will be carried out 6 months after first injection with additional face to face meetings every 6 months thereafter unless the subject requires an additional injection of hylan G-F 20. Hylan G-F 20 treatments can be administered up to three times each year during the study duration. After each injection, follow up measures will be carried out using secure e-mail or phone contact at 6 weeks, 12 weeks, 18 weeks after each in-office evaluation or injection. Follow up will consist of WOMAC, Lysholm score, and Tegner score. . Patients may return for retreatment of hylan G-F 20 if symptoms recur after at least 4 months following their previous injection and they meet the inclusion criteria for pain levels on the following WOMAC questions A1 (How much pain have you had walking on a flat surface?), C8 (How much difficulty have you had going down the stairs?), C9 (How much difficulty have you had when going up the stairs?), C10 (How much difficulty have you had when getting up from a sitting position?) and/or C23 (How much difficulty have you had while doing heavy household chores?). Inclusion criteria for pain level is defined by selecting moderate, severe, or extreme on all questions A1, C8, C9, C10 and/or C23. Those subjects who select mild or no pain levels on any of A1, C8, C9, C10 and/or C23, will not meet the criteria for WOMAC pain level and retreatment. Patients requiring three injections of hylan G-F 20 in 4 months or less will be allowed to exit the cohort after their six-month follow up following the third injection. Otherwise, patients will be followed until they reach the 3 year follow up, or drop out for other injection treatments or surgical treatment. Therefore, patients would potentially be able to receive up to 9 injections during the 3 year study.

Total time for the study will be approximately 8 clinical hours over 3 years, 21 days for the accelerometer test and 4.5 hrs of email/phone contact.

3.2 This experimental Synvisc-One indication is 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).

4 CRITERIA FOR EVALUATION

4.1 Primary Efficacy Endpoint

Co-Primary endpoints

- Proportion of subjects reporting being in PASS during at least one Study Contact Point during entire 36 month study period
- Proportion of Study Contact Points that each subject reports being in PASS during entire 36 month study period

Secondary endpoints

- Change in scores over 36 months for:

- o Worst Knee Pain
- o Five KOOS domains
- o SF-12
- o 12-minute walk test
- o 3-day accelerometer test

The primary endpoint for the study will be analyzed using a responder analysis. The proportion of responders following injection within the 6 months following the baseline injection will be calculated based on Worst Knee Pain scores. A specific timeframe of interest will be the initial 6 months of treatment following the second and any subsequent hylan G-F 20 injection.

4.2 Secondary Efficacy Endpoints

- o Change in scores over 36 months for:
- o Worst Knee Pain
- o Five KOOS domains
- o SF-12
- o 12-minute walk test
- o 3-day accelerometer test

4.3 Safety Evaluations

Adverse reactions will be checked on all phone interviews and clinic visits. Adverse reactions will be captured and tabulated

The most commonly reported related local adverse events were transient, mild-to-moderate arthralgia, arthritis, arthropathy, injection site pain and joint effusion. No serious adverse events were reported in clinical trials in knees injected with Synvisc-One. Serious local adverse events have been reported only rarely in post-marketing use. Repeat treatment did not affect the safety profile. In the pivotal clinical trial, there was one related systemic event of syncope. The most common systemic side effects irrespective of relationship to Synvisc-One were headache, back pain, nasopharyngitis and influenza. Systemic adverse event profiles were similar between patients in the Synvisc-One and Saline Control groups.

5 SUBJECT SELECTION

5.1 Study Population

Subjects with a history of symptomatic unilateral primary or secondary knee OA for more than 6 months, who meet the inclusion and exclusion criteria, will be eligible for participation in this study.

5.2 Inclusion Criteria

Inclusion Criteria:

1. Male or female patients aged 30-50 years
2. History of symptomatic unilateral primary or secondary knee OA for more than 6 months

3. Signed written informed consent
4. Radiographic evidence of Kellgren-Lawrence Grade I or II OA of the target knee
5. Body Mass Index (BMI) < 30 kg/m2
6. Activity criteria (Tegner score > 3)
7. Continued target knee OA pain despite conservative treatment ≥ 3 months (e.g., weight reduction, physical therapy, analgesics)
8. Willing to withhold intake of NSAIDs (including COX-2 inhibitors) and analgesics, for a washout period of minimum 3 days up to 21 days prior to baseline visit (depending on medication)
9. Willing to discontinue prohibited treatments and medications throughout study period Baseline inclusion criteria
10. Completed OA medication washout period
11. Target knee pain 4-8 (0-10 NRS) during most painful knee movement (Worst Knee Pain)
12. If female, must have had a negative urine pregnancy test and used a medically acceptable form of contraception for at least 1 month prior to baseline and agree to continued use of contraception for the duration of the study. Otherwise, females must be surgically sterile, or postmenopausal (as documented in medical history) for at least 1 year. The fetal safety profile for G-F 20 is unknown. Pregnancy will affect the individual's regular activity levels. Females who become pregnant during the study will be excluded from the study. Subjects who become pregnant will be followed up by telephone every 3 months to check for any adverse effects. They will also be recommended to follow routine obstetric visits. Males should be able to father children as it has no expected effects on activity levels.

5.3 Exclusion Criteria:

1. Known allergy to hylan G-F 20 or any of its components, or to avian proteins, eggs, feathers, down, or poultry
2. Clinically apparent tense effusion or other acute inflammation of the target knee at baseline
3. History of target knee viscosupplementation treatment
4. History of major surgery for OA in target knee including arthroplasty or tibial osteotomy
5. Arthroscopic surgery or intra-articular steroid injection in target knee within six months of baseline visit
6. Significant (as judged by the Investigator) alignment deformity of target knee
7. Ipsilateral symptomatic OA of hip or ankle; contralateral symptomatic OA of hip, knee, or ankle
8. History of:
9. Septic OA of any joint
10. Inflammatory arthropathy such as RA, gout, pseudogout, lupus, crystaline inflammatory arthopathy
11. Active infection of lower extremity
12. Known significant acute and/or concurrent medical disease including, but not limited to current malignancy, history of transplant surgery, congestive heart failure,

significant unstable cardiovascular disease, renal hepatic pulmonary, endocrine, metabolic, or GI condition
13. Any known contraindication to acetaminophen
14. Venous or lymphatic stasis in either leg
15. Peripheral vascular disease
16. Patient has been prescribed chronic opioid analgesics at time of baseline visit
17. Concurrent multi-system or multi-limb trauma
18. Patient plans to become pregnant during study period
19. Patient plans to move significantly out of area, have surgery, or initiate or cease other OA treatments
20. Knee pain improves during washout period
21. Workman's Comp patient
22. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.
23. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
24. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

6 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. Patients can receive any other conservative treatments (e.g., oral medications, physical or other therapy, acupuncture, etc., except other injection treatments) and current treatments will be documented during each patient encounter.

6.1 Allowed Medications and Treatments

Patients can receive any other conservative treatments (e.g., oral medications, physical or other therapy, acupuncture, etc., except other injection treatments) and current treatments will be documented during each patient encounter.

7 STUDY TREATMENTS

7.1 Method of Assigning Subjects to Treatment Groups

All subjects in this study will receive the treatment.

7.2 Blinding

Since there is no randomization in this study, blinding will not be necessary,

7.3 Formulation of Test and Control Products

There will be no control products in this study.

7.3.1 Formulation of Test Product

The test product, Synvisc-One, has a unique composition. Synvisc-One, like SYNVISC® , is a mixture of two hylan polymers derived from American and Canadian chicken comb hyaluronan. Hylans are produced by chemically cross-linking hyaluronan in two steps (shown in figure). Synvisc-One is hylan G-F 20, meaning it is 80% hylan A fluid plus 20% hylan B gel. This composition yields a molecular weight and viscoelastic properties that closely match healthy synovial fluid.

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

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

SYNVISC® (hylan G-F 20) and Synvisc-One® (hylan G-F 20) are 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.

7.3.2 Formulation of Control Product

There will be no control or placebo product in this study.

7.3.3 Packaging and Labeling

The package insert is attached. Synvisc-one is supplied in single use boxes that will contain the statement, "CAUTION-Investigational device Limited by Federal law to investigational use." The boxes will be labeled and shipped with this investigational packing to the UCSF Investigational Pharmacy.

7.4 Supply of Study Drug at the Site

Genzyme will ship Synvisc-One to the UCSF Investigational Pharmacy. The initial study drug shipment will be shipped after site activation. For this trial, devices shall be received in M39A, the IDS office. Products are unpacked from shippers by IDS staff, verified against invoice then placed in room temperature storage in M69C, pending transfer to the investigator. If the shipper requires verification of device receipt (fax email, etc.), this will be done at the time of receipt. Subsequent study drug shipments will be made after site request for resupply. The Synvisc-One devices will be couriered to the Orthopaedic Institute on the Mission Bay UCSF campus by the UCSF investigational pharmacy according to subject enrollment by a pharmacy staff member.

Shipping address where all study products will be shipped:

UCSF Inpatient Pharmacy

Attn: Investigational Drugs

505 Parnassus Ave, Room M39C

San Francisco, CA 94143

Pharmacist of Record (PoR):

Scott Fields, PharmD

Investigational Drug Pharmacist

UCSF Inpatient Pharmacy- Attn: Investigational Drugs

505 Parnassus Ave, Room M39C -San Francisco, CA 94143

415 353 1798 (phone) -415 353 8543 (fax)

415 443-9424 (pager)-scott.fields@ucsfmedctr.org

Pharmacist who will assume these responsibilities when the PoR is not available:

Yelena Koplowicz, PharmD

Investigational Drug Pharmacist

UCSF Inpatient Pharmacy- Attn: Investigational Drugs

505 Parnassus Ave, Room M39C -San Francisco, CA 94143

415 353 1798 (phone) -415 353 8543 (fax)

Yelena.Belkin@ucsfmedctr.org

Other pharmacy staff**,** under the direct supervision of the Pharmacist of Record, who may assist with the day-to-day activities:

Christopher Quan, Pharmacy Technician, California licensure

Jane Tam, PharmD, Pharmacist, California licensure

Pharmacy Supervisor:

Courtney Yuen, PharmD, BCOP - Oncology Pharmacy Supervisor

Medical Monitor:
Orthopaedic Institute

Dr. Anthony Luke
Investigator and Medical Monitor
1500 Owens
San Francisco, CA 94158

7.4.1 Dosage/Dosage Regimen

Subjects will receive a single 6 mL intra-articular injection of hylan G-F 20 in the target knee at baseline. Patients can receive any other conservative treatments (e.g., oral medications, physical or other therapy, acupuncture, etc., except other injection treatments) and current treatments will be documented during each patient encounter. An initial injection of hylan G-F 20 will be injected in the symptomatic knee using a standard supine lateral approach using a 20 gauge needle. A face to face follow up visit will be carried out 6 months after first injection with additional face to face meetings every 6 months thereafter unless the subject requires an additional injection of hylan G-F 20. Hylan G-F 20 treatments can be administered up to three times each year during the study duration. After each injection, follow up measures will be carried out using secure e-mail or phone contact at 6 weeks, 12 weeks, 18 weeks after each in-office evaluation or injection. Follow up will consist of WOMAC, Lysholm score, and Tegner score. . Patients may return for retreatment of hylan G-F 20 if symptoms recur after at least 4 months following their previous injection and they meet the inclusion criteria for pain levels on the following WOMAC questions A1 (How much pain have you had walking on a flat surface?), C8 (How much difficulty have you had going down the stairs?), C9 (How much difficulty have you had when going up the stairs?), C10 (How much difficulty have you had when getting up from a sitting position?) and/or C23 (How much difficulty have you had while doing heavy household chores?). Inclusion criteria for pain level is defined by selecting moderate, severe, or extreme on all questions A1, C8, C9, C10 and/or C23. Those subjects who select mild or no pain levels on any of A1, C8, C9, C10 and/or C23, will not meet the criteria for WOMAC pain level and retreatment. Patients requiring three injections of hylan G-F 20 in 4 months or less will be allowed to exit the cohort after their six-month follow up following the third injection. Otherwise, patients will be followed until they reach the 3 year follow up, or drop out for other injection treatments or surgical treatment. Therefore, patients would potentially be able to receive up to 9 injections during the 3 year study.

7.4.2 Dispensing

The Synvisc-One devices will be couriered to the Orthopaedic Institute by the UCSF investigational pharmacy according to subject enrollment by a pharmacy staff member. Upon device transfer from the pharmacy, the investigator shall maintain the devices at controlled room temperature in a designated area in a locked cabinet until they are released for patient administration upon the order of the investigator. The study investigators will administer the injections.

7.4.3 Administration Instructions

The syringe containing SYNVISC (hylan g-f 20) is intended for single use. The contents of the syringe must be used immediately after the syringe has been removed from its packaging. Precaution: Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence. SYNVISC (hylan g-f 20) (2ml) is administered by intra-articular injection once a week (one week apart) for a total of three injections. Strict aseptic administration technique must be followed. Using an 18- to 22-gauge needle, remove synovial fluid or effusion before each SYNVISC (hylan g-f 20) (2ml) injection. Do not use the same syringe for removing synovial fluid and for injecting SYNVISC (hylan g-f 20) however the same 18- to 22-gauge needle should be used. Twist the tip cap before pulling it off, as this will minimize product leakage. To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub. Inject the full 2 mL in one knee only

7.5 Supply of Study Drug at the Site

SYNVISC (hylan g-f 20) is supplied in a 2.25 mL glass syringe containing one 2 mL (16 mg) dose of hylan G-F 20. The contents of the syringe are sterile and non-pyrogenic. The injections will be sent in the standard approved market packaging, with one syringe per box. Replacements will be provided by the manufacturer per site request.

7.5.1 Storage

Investigational Pharmacy

Study devices will be stored in protocol-specific bins on wire rack shelving units in a locked room (M69C) adjacent to the Investigational Drug Service office. Room temperature products are stored in protocol-specific bins on wire rack shelving units in a locked room (M69C) adjacent to the Investigational Drug Service office. Temperature is maintained between 20-25 degrees C. with occasional excursions within the range of 15-30 degrees C. as per the USP definition for Controlled Room Temperature. Two maximum/minimum thermometers (values recorded in whole degree C units) are used to track room temperature, one at the entrance and another at the other end of the storage racks; values are recorded on a daily basis. In addition, a Dickson temperature logger (values recorded every 5 minutes) is used to track temperatures on a continual basis.

The room is also subject to continual monitoring by Awarepoint, a wireless temperature monitoring system that sends text-page alerts to key personnel (pharmacist in charge in the main pharmacy and Investigational Drug Pharmacist) in the event of potential temperature excursions in storage areas. Awarepoint temperature sensors will send a page to the pharmacist in charge in the Inpatient Pharmacy and the PoR in the event of near excursions for all devices monitored by the Awarepoint system: room temperature, refrigerator and -20C freezer. In the event that the alarm is not addressed within 30 minutes, an alert is sent out to the Pharmacy manager on call. Max/min values are recorded daily on a month-specific paper record that is maintained in the room until the end of the month. After this, the records are stored in the IDS files. A copy of the logger readout is downloaded weekly and stored in the same IDS temperature files. The PoR will sign and date the temperature record and the printout of the logger data before filing. The

max/min thermometer at the door also measures relative humidity max/min. These values are recorded on the same record as the max/min temperatures. Reports from the system can be downloaded at any time for documentation of appropriate storage. Temperature monitoring devices are certified annually-biannually.

The PoR will secure the supplies while in possession of the pharmacy. Staff pharmacists have access to investigational agents; a copy of the key to the investigational drug storage room is on the narcotic key ring held by the Central Unit Dose pharmacist or narcotic technician on duty. Additional keys are in the possession of the IDS pharmacist and the Director of Pharmacy and 2 others are maintained in the IDS office, accessible to the Investigational Drug technician and IDS Pharmacists. Staff pharmacists have access to investigational agents; a copy of the key to the investigational drug storage room is on the narcotic key ring held by the Central Unit Dose pharmacist on duty. Additional keys are in the possession of the IDS pharmacist, the Director of Pharmacy and 2 others are maintained in the IDS office, accessible to the Investigational Drug technician and IDS Pharmacists. Limited key distribution as described.

Orthopaedic Institute

Upon transfer from the pharmacy, the investigator shall maintain the devices at controlled room temperature in a designated area in a locked cabinet at 1500 Owens Street until the investigator administrates them. Temperatures in the Orthopaedic Institute are also monitored using the AwarePoint system. AwarePoint enables the Investigational Pharmacy to monitor the Orthopaedic Institute's temperature remotely. Temperature is maintained between 20-25 degrees C. with occasional excursions within the range of 15-30 degrees C. as per the USP definition for Controlled Room Temperature. Study devices will be stored in the clinic until the protocol is closed or until their expiration date has been reached. In those events, those devices shall be returned to the pharmacy for final disposition. The investigator shall be responsible for maintaining the security of the material at the Orthopaedic Institute to prevent unauthorized use. Cabinet key access will be limited to investigators and study key personal.

7.6 Study Drug Accountability

The UCSF investigational pharmacy on the Parnassus campus will be responsible for study drug storage, handling, dispensing, record retention, and return of unused Synvisc-One. Scott Fields, investigational pharmacist, will be responsible for maintaining accurate records about devices received; facilitating the couriering of the devices to the investigative site; and returning devices to manufacturer as needed. An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the pharmacy staff. In supplement to paper based records, this pharmacy uses WebIDS/Vestigo, an internet based drug accountability system. The system will track inventory and expiration dates, generate prescription labels and recharge for services rendered.

At the Orthopaedic Institute, the devices will be locked in a secure cabinet and regularly monitored by Dr. Luke. Dr. Luke and study staff are responsible for maintaining adequate

records of the disposition of the drug including clinical the date, subject number, number of doses and amount dispensed. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

7.7 Measures of Treatment Compliance

A member of the research team will contact the subjects every 6 weeks, either by email or phone, to assess for pain, other treatment history and any adverse events.

8 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

8.1 Clinical Assessments

8.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at each visit. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

8.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at screening visit.

8.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at screening visit.

8.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a sub-investigator who is a physician at the screening visit and visit numbers 2-7. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

8.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes will be performed as needed and during physical examinations.

8.1.6 Standardized X-rays

45° flexion standing weight-bearing, lateral and merchant views x-rays should be completed at or before screening visit

8.1.7 Functional Testing

12-minute walk test, gait analysis, and 3-day accelerometer test will be completed during the screening visit. The walk test involves simple physical movements such as walking and the accelerometer is worn by the patient prior to the visit to measure activity levels. The 12-minute walk test and 3-day accelerometer test will be administered again during their 6 month, 18 month, 24 month, 30 month, and 36 month visits.

8.1.8 Administration of Injection

Using an 18- to 22-gauge needle, the doctor will remove synovial fluid or effusion before each SYNVISC (hylan g-f 20) (2ml) injection. Using an 18- to 22-gauge needle, the doctor will inject the full 2 mL in one knee only.

8.1.10 Concomitant Medication Review

Patient will be asked about any medications they are taking. Current treatments and medications will be documented during each patient encounter.

8.1.11 Email or phone contact

A member of the research team will contact the subjects every 6 weeks, either by email or phone, to assess for pain, other treatment history and any adverse events.

8.1.12 Questionnaires and Assessments

Patients will either complete on their own or be asked questions from the WOMAC, Lysholm-Tegner, Worst Knee Pain, KOOS, and SF-12 assessments by their doctor or another study staff member who will record the appropriate scores during the screening visit. Patients will be assessed again with the Worst Knee Pain, KOOS, SF-12 and WOMAC assessments during their 6month, 18 month, 24 month, 30month, and 36month visits.

8.1.13 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

8.2 Clinical Laboratory Measurements

8.2.1 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study.

9 EVALUATIONS BY VISIT

Baseline Screening (1-3 weeks before Synvisc-One treatment)

- Complete history
- Physical examination

1. History of symptomatic unilateral primary or secondary knee OA for more than 6 months
2. Lysholm-Tegner
3. SF-12
4. WOMAC

Visit 1

- Synvisc-One injection

Visit 2 (6 months post injection)

- Physical examination
- Functional testing:

1.12-minute Walk test
2.3-day accelerometer test

- Evaluation instruments (study questionnaire):

1. Worst Knee Pain
2. KOOS
3. SF-12
4. WOMAC

Visit 3 (12 months post injection)

- Physical examination
- Functional testing:

1. 12-minute Walk test
2. 3-day accelerometer test

- Evaluation instruments (study questionnaire):

1. Worst Knee Pain
2. KOOS
3. SF-12
4. WOMAC

Visit 4 (18 months post injection)

- Physical examination
- Functional testing:

1. 12-minute Walk test
2. 3-day accelerometer test

- Evaluation instruments (study questionnaire):

1. Worst Knee Pain
2. KOOS
3. SF-12
4. WOMAC

Visit 5 (24 months post injection)

- Physical examination
- Functional testing:

1. 12-minute Walk test
2. 3-day accelerometer test

- Evaluation instruments (study questionnaire):

1. Worst Knee Pain

2. KOOS
3. SF-12
4. WOMAC

Visit 6 (30 months post injection)

- Physical examination
- Functional testing:

1. 12-minute Walk test
2. 3-day accelerometer test

- Evaluation instruments (study questionnaire):

1. Worst Knee Pain
2. KOOS
3. SF-12
4. WOMAC

Visit 7 (36 months post injection)

- Physical examination
- Functional testing:

1. 12-minute Walk test
2. 3-day accelerometer test

- Evaluation instruments (study questionnaire):

1. Worst Knee Pain
2. KOOS
3. SF-12
4. WOMAC

Email or phone contact at 6, 12 and 18 weeks post each injection and clinic visit to check for any changes in medical condition.

- Worst Knee Pain (0-10 NRS)
- Other treatment history
- Adverse events

Office Visit	What you do
1-3 weeks before starting study treatment	*Physical exam* *X-ray* *Study questionnaire* *12 minute walk test* *3-day accelerometer test*
Visit 1 - Baseline	*Synvisc-One injection in the affected knee*

Visit 2 – 6 months after injection Visit 3 – 1 year after injection Visit 4 – 1.5 years after injection Visit 5 – 2 years after injection Visit 6 – 2.5 years after *Email or phone contact at 6, 12 and 18 weeks after each injection and office visit*	*Physical exam* *Study questionnaire* *12 minute walk test* *3-day accelerometer test* *Check up on your medical condition*

10 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to Synvisc-One should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death

- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.1.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed. Institution and Investigator understand and agree that Investigator and Institution are obligated under applicable law and regulations to report any serious and related adverse event, if any, that occurs during treatment with the Product to the Institution's IRB and to the governing regulatory authority in accordance with applicable filing timelines promptly after any such event occurs. Prior to or at the time of filing any such report with the governing regulatory authority, Investigator, within 24 hours of first knowledge of such serious and related adverse event, will also transmit an information copy of the report to Genzyme via fax, attention: Genzyme PV, 617-761-8506 or by e-mail to pharmacovigilancesafety@genzyme.com. In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

10.2 Medical Monitoring

Dr. Luke should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: 415-885-3807
Cell: 415-238-7721
Pager: 415-719-8691

11 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

11.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment

- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

11.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

11.3 Replacement of Subjects

Subjects who withdraw from the study treatment in the first 6 months of the study will be replaced. Replacement injected will be requested from Genzyme based on need.

12 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, manufacturer, or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. Dr. Luke will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

13 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

Data Sets Analyzed

The primary endpoint is based on a responder analysis. Response is defined as maintaining a Worst Knee Pain score ≤ 3 on a 0-10 pain scale throughout the 6 months following the baseline injection. Trial success will be based on a non-inferiority test (with 20% non-inferiority threshold) of this response rate in comparison to an external criterion of 70% (Bellamy 2010). Secondary endpoints include determining the duration of response after subsequent injection, determining the effects of treatment on activity levels and quality of life, and describing the three-year time course of each of the study endpoints. The sample size will be n=150 subjects followed for up to 3 years after baseline injection. The power to conclude non-inferiority for a true response rate of 65% is better than 92%.

Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by: race, gender, age, height and weight.

Analysis of Primary Endpoint

The primary endpoint for the study will be analyzed using a responder analysis. The proportion of responders following injection within the 6 months following the baseline injection will be calculated based on Worst Knee Pain scores ≤ 3 on a 0-10 pain scale, which is a threshold consistent with other similar studies (Tubach 2005, Bellamy 2010). The primary endpoint is defined as non-inferiority (with 20% non-inferiority threshold) of the proportion of responders in our study relative to an external criterion of 70% for the responder proportion (Bellamy 2010).

Primary Statistical Analysis: Define the true probability of a subject being a responder as π and the non-inferiority threshold $\delta_{NI} = 0.20$. We require the test of

$$H_0: \pi < 0.70 - \delta_{NI} = 0.50$$

vs. the alternative

$$H_1: \pi \geq 0.70 - \delta_{NI} = 0.50.$$

Non-inferiority will be accepted if the null hypothesis can be rejected with a 2.5% one-sided type I error. To test this hypothesis, we will use the Wilson-Agresti method for a single binomial proportion. Non inferiority will be accepted if the 95% Wilson-Agresti (REF BROWN ET AL 2001) interval for the proportion of responders excludes the null rate of 0.50.

Missing Data: For the analysis of the percentages of positive responders, patients who discontinue the study prior to the Week 26 assessment due to either target knee-related AEs or due to lack of efficacy will be classified as non-responders in the efficacy analysis. Patients who discontinue the study for other reasons will have the responder status imputed using the last observation carried forward (LOCF) method.

Operating Characteristics

The following table shows the power to accept non-inferiority for two assumptions on sample size (n=150 and a smaller sample size reflecting potential dropout of n=120):

True Responder Rate (□.	Sample Size n=150	Sample Size n=120
0.60	72%	61%
0.65	97%	92%
0.70	>99%	>99%
0.75	>99%	>99%

Table 1. Power to conclude non-inferiority for variety of true responder rates and two values for sample size.

Thus, even after conservatively accounting for subject dropout, we will be well-powered to conclude non-inferiority if the true responder rate is at least 65%.

Secondary Outcomes:

- Duration of response to subsequent injections: Though symptoms can be improved for periods up to 6 months, pain symptoms can recur in which case patients will receive a subsequent injection. The duration of these repeated treatments of hylan G-F 20 will be studied.

- Effect of treatment on activity levels and quality of life: The effects of treatment with hylan G-F 20 on activity levels (using objective activity measures utilizing accelerometer

and Physical Activity Enjoyment Scale) and quality of life scores (WOMAC, SF-12) comparing baseline to treatment at 3 months.

- **Three year follow up:** Patients will be followed for up to three years. We will examine the time courses of pain score, activity level, and quality of life over the entire three year span.

Analysis of Secondary Endpoints

Secondary Analyses: Secondary endpoints will be analyzed using confidence intervals as no specific hypothesis tests are being conducted.

The following secondary analyses will be conducted:

- **Duration of response**: Using Kaplan-Meier survival analysis techniques, we will estimate the probability of duration of response over time curve (survival curve) and its confidence limits and also the median duration time and confidence interval. Duration of response analyses will be conducted for the initial injection and also in the subset of patients that receive a follow-up injection.

- **Activity levels and quality of life:** We will estimate the average change and corresponding confidence limits from baseline to 3 months in each of the activity level measures (accelerometer test , walk test, Physical Activity Enjoyment Scale) and the quality of life measures (WOMAC, SF-12). The confidence intervals will be constructed using one sample t-distributions; in the event of strongly skewed measures, we will either use bootstrapping or transformation to construct more accurate intervals. The average change and the endpoints of the confidence intervals can be referenced to external clinically important improvements for comparison.

- **Long term outcome:** We will examine the time course for the pain score, activity level, and quality of life measures across the three years of the study. Estimates and confidence intervals will be derived using mixed effects linear models. Specifically, for each longitudinal outcome measure, we will model it as a function of the (categorical) time point. Intrasubject correlation will be accommodated by either a compound symmetry, autoregressive, or general covariance structure depending on best fit according to BIC. In the event of very non-normally distributed outcomes, we will employ normalizing transformations prior to the analysis. These analyses will be conducted using the Mixed procedure in SAS.

13.5 Interim Analysis

There is no interim analysis planned. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

13.6 Sample Size and Randomization

Bellamy demonstrated in his paper from 2007 (table 3) that a BLISS response at any time during the study was achieved in 70% receiving appropriate care and Hylan G-F 20 and only in 38% of patients receiving appropriate care (P<0.0001). A power calculation using a one-sample comparison of proportion with hypothesized value sample size was performed to determine non-inferiority to the 70% results quoted by Bellamy. Power calculations were measured using STATA's SAMPSI calculator. If we postulate a 20% non-inferiority limit (i.e. that at least 50% of patients receiving G-F 20 will achieve a BLISS response), the sample size required to have 90% power and $\propto$=0.025 to show non-inferiority at 50% would be 70. For a 10% non-inferiority limit with 90% power and $\propto$=0.025, the required sample size is 274, and for 15% non-inferiority limit with 90% power and $\propto$=0.025, it is 124 patients. These numbers do not allow for dropouts, therefore, we intend to recruit 150 subjects to account for dropout.

14 DATA COLLECTION, RETENTION AND MONITORING

Data Collection Instruments

Study personnel will enter data into REDCap (Research Electronic Data Capture). REDCap is a secure, web-based application designed to support data capture for research studies. Subjects will not be identified by name in the study database, but will be identified by a subject number and initials.

14.2 Data Management Procedures

Once data has been successfully entered into the database, the Biostatistics Consulting Unit (BCU) of UCSF's Clinical and Translational Science Institute (CTSI) will perform data management and analysis for the study. Most CTSI personnel have office space within the area occupied by the Department of Epidemiology and Biostatistics at China Basin Landing near UCSF's Mission Bay campus, along with desktop computers and access to departmental "cloud" computing resources. These include secure data storage and access on a HIPAA-compliant server, along with SAS and Stata statistical software. The server room has state-of-the-art environmental controls and security features that include secure, limited access and alarm systems; floor-mount, locking server racks with built-in AC and mounted power strips; dedicated AC unit with temperature monitoring; dedicated circuit breaker and power distribution units; uninterruptible power supply equipment; and fire detection and suppression. Servers are protected by a firewall and anti-virus software. Files and databases are backed up daily. Back-up tapes are sent to an off-site record storage facility every two weeks, with a 2-month tape rotation.

Access to network resources is granted based on documented authorization from a supervisor and permissions are based on user responsibilities. Each user is given a network account consisting of a unique username and a user-designated password that must meet network security criteria. Before network access is given, users are required to train on university electronic security policies. All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

14.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents will be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued.

14.6 Monitoring

Monitoring will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6).

Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on study documentation.

15 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all

applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

Protocol Amendments

Any amendment to the protocol will be submitted by Dr. Luke prior to implementation. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

15.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form has been approved by the will be reviewed and approved by the IRB of the center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB's unconditional approval statement will be transmitted by the Investigator to Genzyme prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

15.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to

the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

15.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).

9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

References

Brown, L. D., T. T. Cai, and A. DasGupta. 2001. Interval estimation for a binomial proportion. Statistical Science 16: 101-133.

APPENDIX 1. SCHEDULE OF STUDY VISITS

	SCREENING	VISIT 1	VISIT 2 6 months	VISIT 3 12 months	VISIT 4 18 months	VISIT 5 24 months	VISIT 6 30 months	VISIT 7 36 months
Informed Consent	X							
Medical History	X							
Complete Physical Exam	x		X	X	x	X	x	x
Abbreviated Physical Exam		x						
Height/weight	x	X	X	X	X	X	X	X
X-rays (flexion, weight bearing, lateral, and merchant views)	x							
Vital Signs	x	x	x	x	x	x	x	x
Motion Gait Analysis	X							
12 Minute Walk Test	X		X	X	X	X	X	X
3-day Accelerometer Test	X		X	X	X	X	X	X
Pregnancy Test	X							
Worst Knee Pain	X		X	X	X	X	X	X
KOOS	X		X	X	X	X	X	X
Lysholm-Tegner	X							
WOMAC	X		X	X	X	X	X	X
SF-12	X		X	X	X	X	X	X
Dispensing or Administration of Study Drug		X						
Concomitant Medication Review	X	X	X	X	X	X	X	X
Adverse Experiences			X	X	X	X	X	X

[a] ±2 days

APPENDIX II

Case Report Forms (Assessments) from the electronic data gathering system, Redcap, are attached.