

**CLINICAL STUDY PROTOCOL**  
**AMENDED VERSION**

**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**

**Protocol Number: SYNV00704**

**Protocol Amendment 2: 19 September 2005**

**Protocol Amendment 1: 12 January 2005**

**Original Protocol: 15 November 2004**

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This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines and the International Organisation for Standardisation (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 Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

I have read and agree to abide by the requirements of this protocol.

Investigator Signature

Date

Investigator Name (please print or type)

## 1. SYNOPSIS

<b>NAME OF COMPANY</b> Genzyme Europe BV Gooimeer 10 1411 DD Naarden The Netherlands	<b>NAME OF FINISHED PRODUCT</b> Synvisc (hylan G-F 20)	<b>NAME OF ACTIVE INGREDIENT</b> N/A
<b>TITLE:</b> 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		
<b>PROTOCOL NO.:</b> SYNV00704		
<b>INVESTIGATOR STUDY SITES:</b> Approximately 20		
<b>OBJECTIVES:</b> To compare the safety and efficacy of 1 x 6-mL intra-articular (IA) injection of Synvisc against 1 x 6-mL IA injection of Placebo (phosphate-buffered saline [PBS]) in treating patients with symptomatic primary osteoarthritis (OA) of the knee.		
<p><b>METHODOLOGY:</b> This is a 2-arm, multi-centre, parallel, double-blind, blinded evaluator, randomised, placebo-controlled clinical study to evaluate the safety and efficacy of a single dose of 6 mL of Synvisc injected IA into the knee. Patients must have documented diagnosis of OA of the target knee made at least 3 months prior to Screening. Patients with bilateral OA of the knees may be enrolled and have 1 knee treated according to the study protocol, as long as the contralateral (non-study) knee can be managed by paracetamol alone. Bilateral OA patients with symptomatic OA of the contralateral knee or either hip that is not responsive to paracetamol and requires other therapy will be excluded from this study.</p> <p>A total of approximately 250 patients will be randomised in this study.</p> <p><u>Study Design/Duration:</u></p> <p>A period of approximately 15 months is anticipated from the time the first patient is enrolled to the completion of the last patient visit (last patient out). Individual patient participation will last up to approximately 8 months.</p> <p><u>Screening Phase:</u></p> <p>At the Screening visit, patients who agree to participate will undergo the informed consent process. After written informed consent is obtained, a Screening number will be assigned and demographic data, height and weight, vital signs, medical history, and prior treatments and medications will be obtained. A physical examination and radiographic assessment of the target knee (if no valid X-ray taken within 3 months prior to Screening is available) will be performed. Radiographic assessment consists of an anteroposterior view: weightbearing (extension or semi-flexion) + profile and a femoro-patellar view at 30° classical. The patient will be instructed to begin the “washout” period of prohibited (pain and OA) medications (i.e., those with half-lives of &gt; 5 hours); from this point forward, none of the prohibited medications are to be taken at any time during the study. The washout period will last for up to 21 days, depending on the half-life of the medications. Baseline (Day 0) should be scheduled between 2 and 21 days after Screening to allow for prohibited medication washout and patient scheduling. Adverse events (AEs) will be collected and recorded from the time the patient signs the informed consent until study completion.</p> <p><u>Treatment Phase:</u></p> <p>Rescue medication for the target knee will consist of paracetamol (up to 4000 mg/day); however, for 48 hours prior to the Day 0 visit, patients are to forego paracetamol and any other pain or OA medications that are otherwise permitted during the study (i.e., those with a half-life of ≤ 5 hours).</p>		

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<p>The patient's eligibility for participation in the study will be re-evaluated at Baseline (Day 0) where it will be confirmed that the patient still meets Screening eligibility criteria and that he/she adhered to the washout period, if required. In addition, each female patient will have a urine pregnancy test, unless she is surgically sterile or postmenopausal (as documented in medical history) for at least 1 year. AEs will be recorded and any new medical findings and changes in medications or treatments will be documented.</p> <p>The patient will complete patient questionnaires at Baseline (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] Likert Scale [LK] Version 3.1, patient global assessment [PTGA]), and the blinded evaluator will complete the clinical observer global assessment (COGA). The same blinded evaluator must complete the COGA for a patient throughout the study. A score of 2 or 3 on the WOMAC LK 3.1 A1 and a mean score of 1.5 to 3.5 on the WOMAC LK 3.1 A is required to qualify for the study.</p> <p>The patient will be randomised to 1 of 2 treatment groups:</p> <p><u>Group 1:</u> Arthrocentesis followed by a 6-mL IA injection of Synvisc on Day 0.</p> <p><u>Group 2:</u> Arthrocentesis followed by a 6-mL IA injection of Placebo (PBS) on Day 0.</p> <p>Patients will be monitored for safety during the treatment phase by the Blinded Evaluator. The evaluator and the patient will be blinded to the treatment group assignment. Unblinded site personnel, such as the Unblinded Injector, will be instructed not to reveal treatment group assignments to blinded personnel or to the patient to ensure that the blinding remains intact. Both study treatment administrations will occur within the specified window.</p> <p><u>Follow-up Phase:</u></p> <p>All patients will return for follow-up within specified visit windows at 1, 4, 8, 12, 18 and 26 weeks following injection. For 48 hours prior to each visit, patients are to forego those pain or OA medications that are otherwise permitted during the study (i.e., those with a half-life of <math>\leq 5</math> hours). In addition, the site will call each patient at 1-week intervals between scheduled visits in order to record data regarding concomitant medications.</p> <p>Safety (but not efficacy) assessments only will be performed at Week 1. Safety and efficacy will be assessed at each patient visit according to the Schedule of Study Events. Efficacy assessments include the WOMAC, PTGA, and COGA questionnaires. Safety assessments will include recording physical examination findings, urine pregnancy test results (for females), concomitant medications and treatments to date, vital signs, and AEs. The evaluator will be reminded to ask the patient if he/she experienced any AEs as a result of the injection.</p> <p>A target knee assessment will be performed at every visit.</p> <p><u>Repeat Treatment Phase:</u></p> <p>After completion of all safety and efficacy assessments at the Week 26 visit, patients will be offered participation in the Repeat Treatment Phase of the study, which will last for an additional 4 weeks. Inclusion criteria will be assessed to determine whether the patient is eligible to receive a course of Synvisc therapy. Should the patient meet these criteria, the injection will be performed on the same day, and all the patients will be placed in the Synvisc treatment arm, regardless of their previous treatment allocation in the Blinded Phase.</p> <p>The same rules and procedures regarding prohibited medications (as described above for the Treatment Phase) will continue to apply throughout the Repeat Treatment Phase.</p>		

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<p>The Repeat Treatment Phase visit schedule and assessment collection will consist of 1 treatment administration visit and follow-up visits for safety at Repeat Weeks 1 and 4. In addition, the site will call each patient at 1-week intervals between scheduled visits in order to record data regarding concomitant medications.</p> <p>Patients will be free to withdraw consent and discontinue study participation at any time and without prejudice to further treatment. In addition, the patient's participation may be discontinued at the discretion of the Investigator or the Sponsor at any time.</p> <p><b>Initial Phase of the Study (Efficacy):</b></p> <p><u>Permitted Treatments and/or Medications:</u></p> <p>The following concomitant treatments and/or medications are permitted:</p> <ul style="list-style-type: none"> <li>○ Any treatment for a pre-existing condition or for an AE, outside of the study indication, that is not listed as prohibited</li> <li>○ Rescue medication for relief of target knee OA pain. Rescue medication is defined as paracetamol up to 4000 mg/day, and patients will then be instructed to discontinue its use 48 hours prior to a study visit</li> <li>○ Other analgesics and analgesic doses of short-acting non-steroidal anti-inflammatory drugs (NSAIDs) with a half-life of <math>\leq 5</math> hours, for indications other than OA pain at the target knee or postinjection local pain management, but not for more than 5 consecutive days or 10 days per month, and not within 48 hours prior to a study visit</li> <li>○ Low-dose aspirin (ASA), 325 mg or less per day, or other platelet aggregation inhibitors (e.g., clopidogrel)</li> <li>○ Topical analgesics/NSAIDs for joints other than the target knee</li> <li>○ Topical corticosteroids for skin irritations at any site except at target knee</li> <li>○ Inhaled corticosteroids for pulmonary disease</li> <li>○ Nonpharmacologic therapy (except physical therapy) for the lower extremities, if begun at least 1 month before Screening, not to be initiated or substantially altered during the study (except for discontinuation)</li> <li>○ Nonpharmacologic therapy (e.g., physical therapy) for joints other than in the lower extremities, or other conditions</li> <li>○ Assistive devices if used throughout a period of 3 months or more prior to Screening, on the condition that they continue to be used throughout the study</li> <li>○ Glucosamine, chondroitin sulfate, diacerhein, or avocado/soya extracts started at least 2 months prior to Screening, not to be initiated or substantially altered during the study</li> </ul> <p><u>Prohibited Treatments and/or Medications:</u></p> <p>The following concomitant treatments and/or medications are prohibited:</p> <ul style="list-style-type: none"> <li>○ Analgesics or NSAIDs other than as described in permitted treatments (e.g., medications with a half-life <math>&gt; 5</math> hours are not permitted at any time during the study but rescue medications, and</li> </ul>		

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<p>those with a half-life of <math>\leq 5</math> hours are permitted except in the 48 hours before a visit)</p> <ul style="list-style-type: none"> <li>○ Chronic use of narcotics</li> <li>○ Systemic corticosteroid(s) (oral or injected)</li> <li>○ Local corticosteroid injection into any joint or periarticular structure in the lower extremities</li> <li>○ Physical therapy for the lower extremities during the study and within a month prior to Screening</li> <li>○ Any surgery of the target knee during the trial</li> <li>○ Heparin or anti-vitamin K (e.g., crystalline warfarin) anticoagulant therapy</li> <li>○ Viscosupplementation injected into any joint other than as required by the protocol</li> <li>○ Any investigational drug, device or biologic used within 3 months prior to Screening and during the study (other than as required by the protocol)</li> </ul> <p><b>Repeat Treatment Phase of the Study (Safety):</b></p> <p><u>Permitted Treatments and/or Medications:</u>                      Same as in Initial Phase (see above).</p> <p><u>Prohibited Treatments and/or Medications:</u>                      Same as in Initial Phase (see above).</p>		
<p><b>NUMBER OF PATIENTS:</b> Approximately 250 (125/group)</p>		
<p><b>DIAGNOSIS/INCLUSION CRITERIA:</b></p> <p><b>Inclusion Criteria:</b></p> <p>A patient may be enrolled in this study if he/she meets all of the following criteria:</p> <p><b>Screening:</b></p> <ol style="list-style-type: none"> <li>1. Provides signed written informed consent</li> <li>2. Is able to read and understand the language and content of the study material, understand the requirements for follow-up visits, and is willing to provide information at the scheduled evaluations</li> <li>3. Is a male or female patient aged 40 years or older</li> <li>4. Is ambulatory, with an active lifestyle, and is in good general health. (Assistive devices are allowed if used throughout a period of 3 months or more prior to Screening, on the condition that they continue to be used throughout the study.)</li> <li>5. Has documented diagnosis of primary OA of the target knee made at least 3 months prior to Screening</li> <li>6. Currently meets American College of Rheumatology (ACR) Criteria for OA as noted below:                         <ul style="list-style-type: none"> <li>○ Knee pain for most days of prior month, and</li> <li>○ Osteophytes at joint margins (radiograph)</li> </ul> </li> </ol>		

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<p>OR</p> <ul style="list-style-type: none"> <li>○ Knee pain for most days of prior month, and</li> <li>○ Synovial fluid typical of OA (laboratory), and</li> <li>○ Morning stiffness ≤ 30 minutes in duration, and</li> <li>○ Crepitus on active joint motion</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>○ Knee pain for most days of prior month, and</li> <li>○ Age ≥ 40 years, and</li> <li>○ Morning stiffness ≤ 30 minutes in duration, and</li> <li>○ Crepitus on active joint motion</li> </ul> <p>7. Has radiographic evidence of OA in the tibio-femoral compartment of the target knee with at least 1 definite osteophyte and a measurable joint space, as diagnosed by standard X-rays<sup>a</sup> taken not longer than 3 months prior to screening, and before any baseline assessment</p> <p>8. Has continued target knee OA pain despite conservative treatment (e.g., weight reduction, physical therapy, analgesics)</p> <p>9. Is willing to withhold intake of NSAIDs (including cyclooxygenase-2 [COX-2] inhibitors) and analgesics, for a washout period of up to 21 days (depending on medication)</p> <p>10. Is willing to discontinue prohibited treatments and medications throughout the study duration</p> <p>11. Is willing to withhold intake of permitted pain medications for 48 hours prior to all study visits</p> <p><sup>a</sup>Anteroposterior view: weightbearing (extension or semi-flexion) + profile and a femoro-patellar view at 30° classical</p> <p><b>Baseline:</b></p> <p>12. If female, must have a negative urine pregnancy test and use a medically acceptable form of contraception for at least 1 month prior to Screening and continue use for the duration of the study. Otherwise, females must be surgically sterile, or postmenopausal (as documented in medical history) for at least 1 year.</p> <p>13. Continues to meet all Screening inclusion/exclusion criteria</p> <p>14. Has completed the pain and OA medication washout period</p> <p>15. Has pain in the target knee as demonstrated by a score of 2 or 3 on the WOMAC LK 3.1 A1</p> <p>16. Has a mean score of 1.5 to 3.5 on the WOMAC LK 3.1 A</p>		

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<p><b>Exclusion Criteria:</b></p> <p>A patient will be excluded from this study if he/she does not meet the specific inclusion criteria, or if he/she is/has:</p> <ol style="list-style-type: none"> <li>1. Modified Kellgren-Lawrence Numerical Grading System of grade IV in the patello-femoral compartment of the target knee confirmed by standard X-rays<sup>a</sup> performed not longer than 3 months prior to Screening, and before any baseline assessment (see definition below):                             <ul style="list-style-type: none"> <li>(IV) Severe: Joint space greatly impaired, with sclerosis of subchondral bone</li> </ul> </li> <li>2. Clinically apparent tense effusion of the target knee</li> <li>3. Significant valgus/varus deformities, ligamentous laxity, or meniscal instability as assessed by the Investigator</li> <li>4. Secondary OA of the target knee</li> <li>5. Viscosupplementation in any joint including the target knee within 9 months prior to Screening</li> <li>6. Had arthroplasty at the target knee at any time or any other previous surgery in the target knee within the 6 months prior to Screening, or planned surgery throughout the duration of the study</li> <li>7. Receiving physical therapy (at an outpatient/clinic setting) for the lower extremities or having received physical therapy for the lower extremities within 1 month before Screening</li> <li>8. History of septic arthritis in any joint</li> <li>9. Concomitant inflammatory disease or other condition that affects the joints (e.g., rheumatoid arthritis, metabolic bone disease, psoriasis, gout, symptomatic chondrocalcinosis and active infection, etc.)</li> <li>10. Symptomatic peripheral vascular disease of the study leg (prior or current)</li> <li>11. Clinically significant venous or lymphatic stasis present in the study leg</li> <li>12. Using protocol-prohibited medication/treatments for chronic pain that patient cannot be withdrawn from prior to study treatment at Baseline and throughout the duration of the study</li> <li>13. Any musculoskeletal condition that would impede measurement of efficacy at the target knee</li> <li>14. Symptomatic OA of the contralateral knee or of either hip that is not responsive to paracetamol and requires other therapy</li> <li>15. Systemic, or IA injection of corticosteroids in any joint within 3 months prior to Screening</li> <li>16. Related hypersensitivities to avian proteins and/or any components of hyaluronan-based injection devices</li> <li>17. Active infection, or history of an infection within the past 12 months, in the area to be injected</li> <li>18. Any significant chronic skin disorder that could interfere with evaluation of the injection site</li> </ol>		

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<ol style="list-style-type: none"> <li>19. Heparin or anti-vitamin K (e.g., crystalline warfarin) anticoagulant therapy</li> <li>20. Any known contraindication to paracetamol</li> <li>21. Started the use of glucosamine, chondroitin sulfate, diacerhein, or avocado/soya extracts within 2 months prior to Screening</li> <li>22. Uncontrolled diabetes mellitus, diabetic neuropathy, or infectious complications; end-stage hepatic or renal disease; or patients on immunosuppressive therapy</li> <li>23. Current malignancy or treatment for malignancy within the past 5 years, except non-melanoma skin cancer</li> <li>24. Active asthma that may require periodic treatment with systemic steroids during the study period (note: inhaled steroids for this condition are allowed)</li> <li>25. Any significant medical condition (e.g., significant psychiatric or neurological disorders, active alcohol/drug abuse, etc.) or other factor (e.g., planned relocation) that the Investigator feels would interfere with study evaluations and study participation</li> <li>26. Used an investigational drug, device, or biologic within 3 months before Screening</li> <li>27. Females who are pregnant, lactating or unwilling to use medically acceptable contraception, or women unwilling to perform a pregnancy test before administration of study treatment</li> <li>28. Ongoing litigation for workers compensation for musculoskeletal injuries or disorders</li> </ol> <p><sup>a</sup>Anteroposterior view: weightbearing (extension or semi-flexion) + profile and a femoro-patellar view at 30° classical</p>		
<p><b>REPEAT TREATMENT PHASE INCLUSION CRITERIA:</b></p> <p>Patients who complete the Week 26 assessments may be enrolled in the Repeat Treatment Phase of this study. <b>In order to receive Synvisc treatment during the Repeat Treatment Phase</b>, patients will be required to meet all of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Must continue to meet Screening Inclusion/Exclusion criteria</li> <li>2. Must have no major safety concerns during the first course of treatment as assessed by the Investigator</li> <li>3. Must have a WOMAC LK 3.1 A score of at least 1</li> <li>4. Must, in the Investigator’s clinical assessment, be a candidate for treatment</li> <li>5. If female, must have a negative urine pregnancy test and continue to use a medically acceptable form 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.</li> </ol>		
<p><b>STUDY INTERVENTION:</b></p> <p><b>Initial Phase:</b></p> <p><b>Group 1:</b> Arthrocentesis followed by a 6-mL IA injection of Synvisc (hylan G-F 20) at Day 0.</p> <p><b>Group 2:</b> Arthrocentesis followed by a 6-mL IA injection of Placebo (PBS) at Day 0.</p>		

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All IA injections must be performed by a qualified Injector other than the Blinded Evaluator. <b>Repeat Treatment Phase:</b> <u>All Eligible Patients:</u> Arthrocentesis followed by a 6-mL IA injection of Synvisc (hylan G-F 20) at Repeat Day 0.		
<b>CRITERIA FOR EVALUATION:</b> <b>Safety:</b> Safety will be determined using the incidence of treatment-emergent AEs, vital signs, and physical examination findings. AEs will be categorised using a standardised coding dictionary (e.g., Medical Dictionary for Regulatory Activities [MedDRA]). <b>Efficacy:</b> <u>Primary Efficacy Objective</u> To demonstrate that 1 x 6-mL injection of Synvisc provides superior pain relief (WOMAC LK 3.1 A) over 26 weeks as compared to a 1 x 6-mL IA injection of Placebo (PBS) in treating patients with symptomatic primary OA of the knee. <u>Secondary Efficacy Objectives</u> <ul style="list-style-type: none"> <li>• To analyse the differences between the WOMAC A subscore from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group.</li> <li>• To analyse the differences between the WOMAC A1 subscore over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group.</li> <li>• To analyse the differences between the WOMAC C subscore over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group.</li> <li>• To analyse the differences between the PTGA over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group.</li> <li>• To analyse the differences between the COGA over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group.</li> <li>• To analyse the differences between the percentages of positive responders to treatment for symptomatic primary OA of the knee over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group (where response is defined with the OMERACT OARSI set of responder criteria [<a href="#">Pham, 2003, J of Rheumatol</a>; <a href="#">Pham, 2004, Osteoarthritis Cartilage</a>]).</li> </ul> <u>Tertiary Efficacy Objectives:</u> <ul style="list-style-type: none"> <li>• To analyse the differences between the Total WOMAC score over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group</li> <li>• To analyse the differences between the WOMAC B subscore over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS)</li> </ul>		

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<p>group</p> <ul style="list-style-type: none"> <li>To analyse the differences between the average daily consumption of paracetamol (grams) over 26 weeks in the Synvisc treatment group and the Placebo (PBS) group</li> </ul>		
<p><b>STATISTICAL METHODS:</b></p> <p><b>Safety:</b></p> <p>The safety analyses will be performed on the Safety Population defined as all patients who undergo the first injection. Treatment-emergent AEs will be summarised by treatment group and categorised by severity and relationship to the study procedures. Treatment-emergent AEs will be summarized both including and excluding AEs generated from deteriorations noted in the target knee assessment (if any). Target knee AEs also will be summarized separately. If a patient has more than 1 occurrence of the same AE, he/she will be 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, will be indicated in cases of multiple occurrences of the same AE. All AEs will be presented in a listing. Additionally listings of serious adverse events (SAEs) and AEs leading to discontinuation will be generated.</p> <p>Vital signs and physical examination findings will be tabulated. Concomitant medications and treatments will be categorised using a standardised coding dictionary (e.g., MedDRA, World Health Organisation Drug Dictionary [WHO-drug]) and summarised.</p> <p>For the Repeat Treatment Phase of the study, all treatment-emergent AEs will be summarised.</p> <p><b>Efficacy:</b></p> <p><u>Primary Efficacy Analysis</u></p> <p>The primary efficacy analysis will be performed on the Intent-to-Treat (ITT) Population, which will include all patients randomised, and will be based on a repeated measures model that will be used to test for differences in treatment efficacy, as quantified by the WOMAC LK 3.1 A subscore over 26 weeks between Synvisc and Placebo (PBS). The test of treatment efficacy will be constructed using least-square mean estimates (linear combinations of the estimated regression parameters). Missing efficacy data will be imputed using the Last Observation Carried Forward (LOCF) method.</p> <p>The primary efficacy analysis may be repeated on the Per-Protocol Population, which will exclude all patients with major protocol violations.</p> <p><u>Secondary and Tertiary Efficacy Analysis</u></p> <p>As with the primary efficacy analysis, the secondary efficacy analyses will be performed on the ITT Population. For the analysis of the WOMAC A, WOMAC B, WOMAC C, Total WOMAC, PTGA, and COGA, a repeated-measures linear model will be used as described in the description of the primary efficacy analysis.</p> <p>For the analysis of the percentages of positive responders, logistic regression modelling and generalised estimating equations (GEE) modelling will be used. Using the Baseline and follow-up data, patients will be defined as responders or non-responders based on the OMERACT-OARSI set of criteria (Pham, 2003, <i>Journal of Rheumatology</i>; Pham, 2004, <i>Osteoarthritis Cartilage</i>). The binary classification (response, no response) will be used in the logistic regression modelling, which will include covariates for treatment group assignment and relevant baseline covariates, to analyse the differences between the</p>		

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<p>percentages of positive responders from Baseline to each post-Baseline assessment in the Synvisc treatment group and the Placebo (PBS) group. A Wald test based on the estimated regression parameter for treatment group assignment will provide the basis for the hypothesis testing. Differences in the percentages of positive responders over 26 weeks in the Synvisc treatment group and the Placebo (PBS) group will be analysed with GEE. For each post-Baseline study visit, patients will be defined as responders or non-responders based on the OMERACT-OARSI set of criteria. These repeated binary outcomes (responders/non-responder) will be modelled with GEE and a Wald test based on the estimated regression parameter for treatment group assignment will provide the basis for hypothesis testing for this secondary efficacy objective.</p> <p>Paracetamol usage and the WOMAC A1 (overall 26-week difference and the change from Baseline to Week 26) will be analysed using 2-sample t-tests.</p> <p>Figures illustrating the longitudinal response profiles of the Synvisc and Placebo (PBS) groups for the efficacy variables will be provided. Tables summarizing the efficacy variables including the sample size, mean, median, SD, and range, will be presented.</p> <p><b>Power and Sample Size:</b></p> <p>Approximately 250 patients with symptomatic primary OA of the knee will be randomised. Sample size estimation is based on using the mean difference in the WOMAC LK 3.1 A change from Baseline in the primary efficacy analysis. The following assumptions were made to compute the sample size:</p> <ul style="list-style-type: none"> <li>• The 2-sample t-test comparing the within-treatment group means of the patient-specific mean change from Baseline is used. The 2-sample t-test approximates the test of the null hypothesis based on the repeated measures model that will be used in the primary efficacy analysis.</li> <li>• Overall treatment difference of 0.297</li> <li>• Common standard deviation (SD) of 0.725</li> <li>• Dropout rate of 25%</li> <li>• Two-sided significance level of 5%</li> </ul> <p>With these assumptions, a sample size of approximately 250 patients (125 patients per treatment arm) provides over 80% power to detect an overall difference of 0.297 (WOMAC LK 3.1 A) between the Synvisc treatment group and the Placebo (PBS) group over the course of 26 weeks.</p>		

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### 3. ABBREVIATIONS AND TERMS

#### 3.1 List of Abbreviations

ACR	American College of Rheumatology
AE	Adverse event
AP	Anteroposterior
ASA	Acetylsalicylic acid; aspirin
COGA	Clinical Observer Global Assessment
COX-2 inhibitors	Cyclooxygenase-2 inhibitors
CPRS	Clinical Pharmacy Research Services
CSSF	Clinical Supply Shipment Form
CTM	Clinical Trial Material
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ePQ	Electronic Patient Questionnaire
GCP	Good Clinical Practice
GEE	Generalised estimating equations
HA	Hyaluronic acid; sodium hyaluronate; hyaluronan
HEENT	Head, Ears, Eyes, Nose and Throat
IA	Intra-articular
ICH	International Conference on Harmonisation
ID	Identification
ISO	International Organisation for Standardisation
ITT	Intent-to-Treat
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Millilitre
mm	Millimetre
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis

OMERACT-OARSI	Outcome Measures in Rheumatology-Osteoarthritis Research Society International
PBS	Phosphate-buffered saline, which has the same formulation as the diluent for Synvisc (buffered physiological sodium chloride solution [pH 7.2 ± 0.3])
PTGA	Patient Global Assessment
QA	Quality Assurance
SAE	Serious adverse event
SAS <sup>®</sup>	Statistical Analysis Systems
SD	Standard deviation
WHO-drug	World Health Organisation Drug Dictionary
WOMAC LK 3.1	Western Ontario and McMaster Universities Osteoarthritis Index Likert Scale Version 3.1

#### 4. INTRODUCTION

Osteoarthritis (OA) is the most common joint disease and one of the most frequent causes of physical impairment (Altman, 1987, *Am J Med*). A critical element contributing to the pathophysiology of OA is the loss of the elastic and viscous properties of the synovial fluid during the course of the disease. This diminished elastoviscosity of the synovial fluid alters the mechanical force transmission to the cartilage, increasing its susceptibility to mechanical damage or wear and tear. The loss of elastoviscosity of the synovial fluid in OA is due to a decrease in the molecular weight and concentration of hyaluronan (hyaluronic acid, HA), a glycosaminoglycan that is responsible for the lubricating and shock absorption properties of the synovial fluid (Balazs, 1967, *Arthritis Rheum*; Balazs, 1993, *J Rheumatol Suppl*).

Viscosupplementation is a therapeutic technique that directly addresses the cause of pain by replacing the low elastoviscous osteoarthritic synovial fluid with high elastoviscous solutions of hyaluronan or its derivatives.

Synvisc was approved for the treatment of pain associated with knee OA in Canada (1992), Sweden (1995), the European Economic area (1995), the United States (1997) and many other countries. Synvisc, a high molecular weight, cross-linked derivative of hyaluronan (extract of chicken comb), is an injection regimen involving 3 IA injections. Synvisc is composed of both cross-linked gel and unmodified HA in a physiological buffered saline (in a 20:80 gel: fluid ratio).

Currently, the recommended dosing regimen of Synvisc for the treatment of knee OA pain is 3 x 2-mL IA injections, where 3 separate 2-mL injections are each administered 1 week apart. The peak efficacy of Synvisc under this regimen appears between 8 to 12 weeks after the administration of the first injection, and can have a duration of 6 to 12 months.

Anecdotal reports, however, from physicians having used fewer injections and/or longer time intervals between injections in the treatment of knee OA patients suggested alternate dosing regimens may also be of benefit to the patient.

Based on these observations, further studies were conducted in order to assess the safety and efficacy of several alternate dosing regimens and re-treatment, as described in [Section 8.5](#). These additional data served as the rationale for the choice of the 1 x 6-mL dosing scheme used in the current study, Genzyme study SYNV00704. This study will assess the safety and efficacy of a single, 6-mL IA injection of Synvisc against a single, 6-mL IA injection of Placebo (PBS) in treating patients with symptomatic OA of the knee over 26 weeks of follow-up. In addition, the safety of a repeat treatment of a single, 6-mL injection of Synvisc will also be assessed.

## **5. STUDY OBJECTIVES**

To compare the safety and efficacy of 1 x 6-mL IA injection of Synvisc against 1 x 6-mL IA injection of Placebo (PBS) in treating patients with symptomatic primary OA in the knee.

## 6. INVESTIGATIONAL PLAN

### 6.1 Study Design

This is a 2-arm, multi-centre, parallel, double-blind, blinded evaluator, randomised, placebo-controlled clinical study to evaluate the safety and efficacy of a single dose of 6 mL of Synvisc injected IA into the knee. Patients must have documented diagnosis of primary OA of the target knee made at least 3 months prior to Screening. A patient will be excluded from the study if he/she has either symptomatic OA of the contralateral knee OR has symptomatic OA of either hip that is not responsive to paracetamol and requires other therapy.

A total of approximately 250 patients will be randomised in this study.

A period of approximately 15 months is anticipated from the time the first patient is enrolled to the completion of the last patient visit (last patient out). Individual patient participation will last up to approximately 8 months.

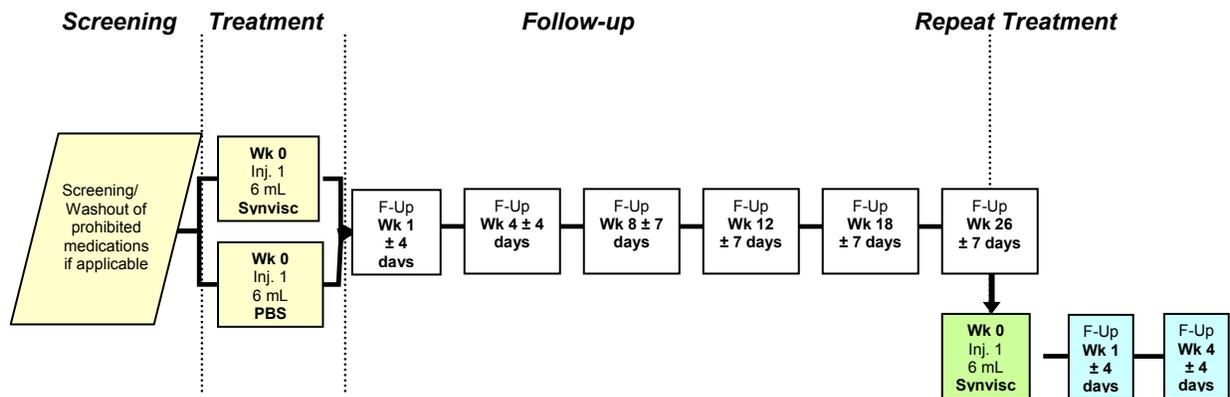
Eligible patients will be randomised to 1 of 2 treatment arms. Patients assigned to Group 1 will receive arthrocentesis followed by a 6-mL IA injection of Synvisc on Day 0; and Group 2 will receive arthrocentesis followed by a 6-mL IA injection of Placebo (PBS) on Day 0 (to maintain the treatment blinding).

Patients will be monitored for safety during the treatment phase by the Blinded Evaluator. The evaluator and the patient will be blinded to the treatment group assignment. Unblinded site personnel, such as the Unblinded Injector, will be instructed not to reveal treatment group assignments to blinded personnel or to the patient to ensure that the blinding remains intact. Both study treatment administrations will occur within the specified window.

Patients may not use any of the prohibited pain medications at any time during the study. Rescue medication for the target knee will consist of paracetamol (up to 4000 mg/day) and is not to be taken within 48 hours prior to study visits. In addition, patients are to forego other permitted pain medications (i.e., those with half-lives  $\leq 5$  hours) for 48 hours prior to study visits.

Figure 1 illustrates the study design for each dosing arm.

**Figure 1 Study Design for Each Dosing Arm**



### 6.1.1 Enrolment

A total of approximately 250 patients will be enrolled and randomised in this study.

### 6.1.2 Screening Phase

At the Screening visit, patients who agree to participate will undergo the informed consent process. Patients must be provided with sufficient information and be allowed adequate time in which to decide whether they will participate. After written informed consent is obtained, a Screening number will be assigned (refer to [Section 8.4](#)) and demographic data, height and weight, vital signs (blood pressure, heart rate and temperature), medical history, and prior treatments and medications will be obtained. A physical examination and radiographic assessment of the target knee (if an X-ray taken within 3 months prior to Screening is not available) will be performed. If the patient has not had a valid X-ray taken within 3 months prior to Screening, an anteroposterior (AP) view: weightbearing (extension or semi-flexion) + profile and a femoro-patellar view at 30° classical will be obtained at Screening.

Sites will be allowed 1 opportunity to re-screen each patient. If the patient subsequently screen fails, then he/she can no longer be considered for entry into the study. Refer to [Section 8.4](#) for details.

The patient will be instructed to begin the “washout” period of prohibited pain and OA medications (i.e., those with half-lives of > 5 hours, see [Table 9-4](#)); from this point forward, none of the prohibited medications are to be taken at any time during the study. The washout period will last for up to 21 days, depending on the half-life of the medications. Baseline

(Day 0) should be scheduled between 2 and 21 days after Screening to allow for prohibited medication washout, and patient scheduling. AEs will be collected and reported from the time the patient signs the informed consent until study completion.

#### **6.1.2.1 Rescue Medications**

Patients will be allowed to take rescue medication (paracetamol, not to exceed 4000 mg/day) for target knee pain relief throughout the duration of the trial, including during the Screening phase, with the exception of within 48 hours prior to study evaluations. Other permitted pain medications (i.e., those with half-lives  $\leq 5$  hours) are listed in [Table 14-1](#).

#### **6.1.3 Treatment Phase**

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

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

The patient will complete patient questionnaires at Baseline (WOMAC LK 3.1, PTGA), and the blinded evaluator will complete the COGA. The same blinded evaluator must complete the COGA for a patient throughout the study. A mean score of 1.5 to 3.5 on the WOMAC LK 3.1 A and a score of 2 or 3 on the WOMAC LK 3.1 A1 is required to qualify for the study.

#### **6.1.3.1 Randomisation**

Once Baseline eligibility criteria have been met, the patient will be randomised to 1 of 2 treatment groups:

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

The evaluator and the patient will be blinded to the treatment group assignment. Unblinded site personnel, such as the Unblinded Injector, will be instructed not to reveal treatment group assignments to blinded personnel or to the patient to ensure that the blinding remains intact. Both study treatment administrations will occur within the specified window.

### **6.1.3.2 Study Material Administration**

If a patient has clinically apparent tense effusion at the target knee at Baseline (following washout), he/she will be considered a screen failure (see [Section 8.4](#)) and may be rescheduled to return to the site within the allowed time window ([Table 9-3](#)) and instructed by the site staff on how to prepare for the return visit. If at the time of the return visit, the patient still has clinically apparent tense effusion at the target knee, he/she will be discontinued from study participation. If the tense effusion has resolved, the patient may continue to participate in the study.

The IA injection of study material will be administered by a qualified professional (Unblinded Injector) experienced in administering IA injections (see [Section 6.3](#) for Site Staffing Requirements). The evaluator and the patient will be blinded to the treatment group assignment. A surgical drape will be placed so as to shield the patient's knee and the study treatment from his/her view during the procedure. Unblinded site personnel will be instructed not to reveal treatment group assignments to blinded personnel or to the patient to ensure that the blinding remains intact. The study treatment administration will occur within the specified window (see [Table 9-3](#)). See [Section 8](#) for Instructions on Clinical Trial Material Administration.

### **6.1.4 Follow-up Phase**

All patients will return for follow-up within specified visit windows at 1, 4, 8, 12, 18 and 26 weeks following injection. For 48 hours prior to each visit, patients are to forego those pain or OA medications that are otherwise permitted during the study (i.e., those with a half-life of  $\leq 5$  hours). The site will call each patient at 1-week intervals between scheduled visits in order to record data regarding concomitant medications. Data collected will include the product name, the exact dose, the days of intake and the indication. The call itself (date and time) as well as the information collected will be recorded on a specific worksheet provided by the Sponsor to the site. This information will then be transcribed onto the eCRF and the worksheet will remain onsite in the patient's medical records and will be considered as a source document.

Safety (but not efficacy) assessments will be performed at Week 1. Safety and efficacy will be assessed at each patient visit according to the Schedule of Study Events. Efficacy assessments include the WOMAC, PTGA, and COGA questionnaires. Safety assessments will include recording physical examination findings, urine pregnancy test results (for females), concomitant medications and treatments to date, vital signs, and AEs. The evaluator will be reminded to ask the patient if he/she experienced any AEs as a result of the injection.

A target knee assessment will be performed at every visit.

At all follow-up visits after Week 1, the patient will complete patient questionnaires (WOMAC LK 3.1 and PTGA). After the patient questionnaires are completed, the Blinded Evaluator will complete the COGA (the same blinded evaluator must complete the COGA for a patient throughout the study).

Concomitant medications and treatments, and AEs will be recorded at all visits and any new medical findings and changes in medications will be documented. Vital signs will be obtained at Week 26. A physical examination and urine pregnancy test (if applicable) will be performed at Week 26. Safety and efficacy assessments at each patient visit are summarised in the Schedule of Study Events ([Table 9-1](#)).

Any patient who discontinues prematurely after receiving at least 1 IA injection of either study material must complete all final (Week 26) evaluations at the time of discontinuation.

#### **6.1.5 Repeat Treatment Phase**

The primary goal of the Repeat Treatment Phase is to evaluate safety in patients receiving a second, repeat treatment of Synvisc at 26 weeks following the first course of treatment. Therefore, after completion of all safety and efficacy assessments at the Week 26 visit, patients will be offered participation in the Repeat Treatment Phase of the study, which will last for an additional 4 weeks. The same rules and procedures regarding prohibited medications (as described in [Section 6.1.7](#)) will continue to apply throughout the Repeat Treatment Phase. At the Week 26 visit, the Repeat Treatment Phase inclusion criteria listed in [Section 7.3](#) will be assessed to determine whether the patient is eligible to receive a course of Synvisc therapy. Patients meeting the eligibility criteria will be treated that same day, i.e., at the Week 26 visit, which would in that case be synonymous with Repeat Treatment Day 0 visit.

Patients will receive study material administration at the Repeat Week 0 visit as summarised in [Table 9-2](#). Patients will be assessed for safety following repeat treatment.

The Repeat Treatment Phase visit schedule and study assessments will consist of 1 treatment administration visit (as described above) and follow-up visits for safety at Repeat Weeks 1 and 4. Refer to [Table 9-2](#) for procedures and assessments to be performed at each Repeat Treatment Phase visit. Rescue medication for the target knee will consist of paracetamol (not to exceed 4000 mg/day) and not to be taken within 48 hours prior to study visits. In addition, the site will call each patient at 1-week intervals between scheduled visits in order to record data regarding concomitant medications.

Patients will be free to withdraw consent and discontinue study participation at any time and without prejudice to further treatment. In addition, a patient's participation in the study may be discontinued at the discretion of the Investigator or Sponsor at any time.

#### **6.1.6 Permitted Treatments and/or Medications – Initial Phase of the Study (Efficacy)**

The following concomitant treatments and/or medications are permitted during the study:

- Any treatment for a pre-existing condition or for an AE, outside of the study indication, that is not listed as prohibited
- Rescue medication for relief of target knee OA pain. Rescue medication is defined as paracetamol up to 4000 mg/day, and patients will then be instructed to discontinue its use 48 hours prior to a study visit
- Other analgesics and analgesic doses of short-acting NSAIDs (with a half-life  $\leq 5$  hours) for indications other than OA pain at the target knee or postinjection local pain management, but not for more than 5 consecutive days or 10 days per month, and not within 48 hours prior to a study visit
- Low-dose ASA, 325 mg or less per day, or other platelet aggregation inhibitors (e.g., clopidogrel)
- Topical analgesics/NSAIDs for joints other than the target knee
- Topical corticosteroids for skin irritations at any site except at target knee
- Inhaled corticosteroids for pulmonary disease
- Nonpharmacologic therapy (except physical therapy) for the lower extremities, if begun at least 1 month before Screening, not to be initiated or substantially altered during the study (except for discontinuation)
- Nonpharmacologic therapy (e.g., physical therapy) for joints other than in the lower extremities, or other conditions
- Assistive devices if used for 3 months or more prior to Screening, on the condition that they continue to be used throughout the study
- Glucosamine, chondroitin sulfate, diacerhein, or avocado/soya extracts started at least 2 months prior to Screening, not to be initiated or substantially altered during the study

Permitted concomitant treatments and/or medications are summarised below in Table 6-1.

**Table 6-1 Permitted Treatments and/or Medications**

<b>Treatments Allowed</b>	<b>Restriction</b>
Any treatment for a pre-existing condition or for an AE, outside the study indication, that is not listed as prohibited	Treatments cannot be prohibited per protocol
Rescue medication: paracetamol	Rescue medication only, but not to exceed 4000 mg/day. Not within 48 hours prior to study evaluation. Patients will be instructed not to take medications (other than rescue medications) for target knee OA pain relief.
Low-dose ASA, or other platelet aggregation inhibitors (e.g., clopidogrel)	Not to exceed 325 mg/day
Other analgesics or analgesic doses of short-acting NSAIDs (half-life $\leq$ 5 hours) for indication <b>other than OA at the target knee or for postinjection local pain management</b>	Do not exceed recommended dosing in product information. Not taken for more than 5 consecutive days Not taken for more than 10 days/month Not within 48 hours prior to a study visit
Topical analgesics/NSAIDs for joints	Allowed at any site other than the target knee
Topical corticosteroids for skin irritations	Allowed at any site other than the target knee
Inhaled corticosteroids for pulmonary disease	None
Nonpharmacologic therapy (except physical therapy) for the lower extremities	Allowable if started $\geq$ 1 month before Screening, not to be initiated or substantially altered during the study except for discontinuation
Nonpharmacologic therapy (e.g., physical therapy) for joints other than in the lower extremities, or other conditions	Allowed without restriction at any site other than the lower extremities (see line above)
Assistive devices	Allowable if used $\geq$ 3 months before Screening and will continue to be used throughout the study
Glucosamine, chondroitin sulfate, diacerhein, or avocado/soya extracts	Allowable if started at least 2 months before Screening, not to be initiated or substantially altered during the study

**6.1.7 Prohibited Treatments and/or Medications – Initial Phase of the Study (Efficacy)**

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

- Analgesics or NSAIDs other than as described in permitted treatments (e.g., medications with a half-life  $>$  5 hours are not permitted at any time during the study but rescue medications, and those with a half-life of  $\leq$  5 hours are permitted except in the 48 hours before a visit)
- Chronic use of narcotics
- Systemic corticosteroid(s) (oral or injected)

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

Prohibited concomitant treatments and/or medications are summarised below in Table 6-2.

**Table 6-2 Prohibited Treatments and/or Medications**

Medication Not Allowed	Restriction
Analgesics or NSAIDs other than as described in permitted treatments	Beginning at Screening and lasting throughout the duration of the trial (or study discontinuation)
Chronic use of narcotics	
Systemic corticosteroid(s) (oral or injected)	
Local corticosteroid injection into any joint or periarticular structure in the lower extremities	
Any surgery of the target knee during the trial	
Heparin or anti-vitamin K (e.g., crystalline warfarin) anticoagulant therapy	
Viscosupplementation injected into any joint other than as required by the protocol	
Any investigational drug, device or biologic	Within 3 months prior to Screening and lasting throughout the duration of the trial (other than as required by the protocol)
Physical therapy for the lower extremities	Within a month prior to Screening and lasting throughout the duration of the trial (or until study discontinuation)

**6.1.8 Permitted and Prohibited Treatments and/or Medications – Repeat Phase of the Study**

The rules regarding concomitant treatments and/or medications are the same as those described for the treatment phase of the study (see Sections 6.1.6 and 6.1.7).

## 6.2 Study Duration

A period of approximately 15 months is anticipated from the time the first patient is enrolled to the completion of the last patient visit (last patient out). Individual patient participation will last up to approximately 8 months.

## 6.3 Site Staffing Requirements

The Investigator is responsible for ensuring that he/she has sufficient and appropriate staff to conduct the clinical trial and that all study-related tasks have been appropriately delegated and documented. There must be at least the following study staff at each site:

- **Blinded Evaluator** must be a medical doctor (e.g., orthopaedic surgeon, rheumatologist, physiotherapist, etc.), physician's assistant, or registered nurse or equivalent, and must have relevant orthopaedic experience. The Blinded Evaluator is responsible for questioning and examining the patient at each study visit and to administer the relevant questionnaires to the patient. The Blinded Evaluator will perform all Screening, Baseline and follow-up procedures, complete a COGA and may be responsible for additional study procedures (e.g., assessing AEs), as long as, he/she remains blinded to the study treatment. The same blinded evaluator should complete the COGA for a patient throughout the study. However, only the Investigator may assess the causality of an AE or SAE.
- **Unblinded Injector** must be a medical doctor (e.g., radiologist, orthopaedic surgeon, rheumatologist, physiotherapist, or other physician experienced in administering IA injections), or a physician's assistant (at the discretion of the Investigator). The Unblinded Injector will perform all injections for a given patient. The Unblinded Injector will be instructed not to share treatment assignments with the Blinded Evaluator or the patient. The number of Unblinded Injectors at a given site will be limited to 2.

If a study coordinator is available, depending on qualifications, he/she may serve either role, as well. Having 1 site staff member serve as the Blinded Evaluator for 1 patient and then as the Unblinded Injector for another patient is not permitted. All site staff and their study responsibilities will be documented on the Signature and Responsibility Log provided by the Sponsor.

## 6.4 Discussion of Study Design Including Choice of Control Group

Viscosupplementation consists of replacement of arthritic synovial fluid with hyaluronan or its derivatives, restoring the physiological and rheological states of arthritic joints. Synvisc is a sterile, nonpyrogenic, synovial viscosupplement intended for the treatment of pain associated with OA of the knee. Synvisc is administered by IA injection into the knee joint through an 18- to 20-gauge needle.

There are limited comparator options for local administration of IA therapy for knee OA. IA injection of PBS was selected as the comparator because it facilitates study blinding and because it has the same formulation as the diluent in Synvisc (buffered physiological sodium chloride solution [pH 7.2 ± 0.3]).

## 7. PATIENT POPULATION AND SELECTION

Approximately 250 patients with symptomatic primary OA of the knee will be randomised. This sample size assumes a patient discontinuation rate due to target knee AEs or lack of efficacy of 10% in each group and a dropout rate for reasons other than target knee AEs and lack of efficacy of 15% in each group.

### 7.1 Inclusion Criteria

A patient may be enrolled in this study if he/she meets all of the following criteria:

#### Screening:

1. Provides signed written informed consent
2. Is able to read and understand the language and content of the study material, understand the requirements for follow-up visits, and is willing to provide information at the scheduled evaluations
3. Is a male or female patient aged 40 years or older
4. Is ambulatory with an active lifestyle and in good general health. (Assistive devices are allowed if used throughout a period of 3 months or more prior to Screening, on the condition that they continue to be used throughout the study.)
5. Has documented diagnosis of primary OA of the target knee made at least 3 months prior to Screening

6. Currently meets ACR Criteria for OA as noted below:

- Knee pain for most days of prior month, and
- Osteophytes at joint margins (radiograph)

OR

- Knee pain for most days of prior month, and
- Synovial fluid typical of OA (laboratory), and
- Morning stiffness  $\leq$  30 minutes in duration, and
- Crepitus on active joint motion

OR

- Knee pain for most days of prior month, and
- Age  $\geq$  40 years, and
- Morning stiffness  $\leq$  30 minutes in duration, and
- Crepitus on active joint motion

7. Has radiographic evidence of OA in the tibio-femoral compartment of the target knee with at least 1 definite osteophyte and a measurable joint space, as diagnosed

by standard X-rays<sup>a</sup> taken not longer than 3 months prior to screening, and before any baseline assessment

8. Has continued target knee OA pain despite conservative treatment (e.g., weight reduction, physical therapy, analgesics)
9. Is willing to withhold intake of NSAIDs (including COX-2 inhibitors) and analgesics, for a washout period of up to 21 days (depending on medication)
10. Is willing to discontinue prohibited treatments and medications throughout the study duration
11. Is willing to withhold intake of permitted pain medications for 48 hours prior to all study visits

<sup>a</sup>Anteroposterior view: weightbearing (extension or semi-flexion) + profile and a femoro-patellar view at 30° classical

### **Baseline:**

12. If female, must have a negative urine pregnancy test and use a medically acceptable form of contraception for at least 1 month prior to Screening and continue use for the duration of the study. Otherwise, females must be surgically sterile, or postmenopausal (as documented in medical history) for at least 1 year.
13. Continues to meet all Screening inclusion/exclusion criteria
14. Has completed the pain and OA medication washout period
15. Has pain in the target knee as demonstrated by a score of 2 or 3 on the WOMAC LK 3.1 A1
16. Has a mean score of 1.5 to 3.5 on the WOMAC LK 3.1 A

## **7.2 Exclusion Criteria**

A patient will be excluded from this study if he/she does not meet the specific inclusion criteria, or if he/she is/has:

1. Modified Kellgren-Lawrence Numerical Grading System of grade IV in the patello-femoral compartment of the target knee confirmed by standard X-rays<sup>a</sup> performed not longer than 3 months prior to Screening, and before any baseline assessment (see definition below):  
(IV) Severe: Joint space greatly impaired, with sclerosis of subchondral bone
2. Clinically apparent tense effusion of the target knee
3. Significant valgus/varus deformities, ligamentous laxity, or meniscal instability as assessed by the Investigator
4. Secondary OA of the target knee
5. Viscosupplementation in any joint including the target knee within 9 months prior to Screening

6. Had arthroplasty at the target knee at any time or any other previous surgery in the target knee within the 6 months prior to Screening, or planned surgery throughout the duration of the study
7. Receiving physical therapy (at an outpatient/clinic setting) for the lower extremities or having received physical therapy for the lower extremities within 1 month before Screening
8. History of septic arthritis in any joint
9. Concomitant inflammatory disease or other condition that affects the joints (e.g., rheumatoid arthritis, metabolic bone disease, psoriasis, gout, symptomatic chondrocalcinosis and active infection, etc.)
10. Symptomatic peripheral vascular disease of the study leg (prior or current)
11. Clinically significant venous or lymphatic stasis present in the study leg
12. Using protocol-prohibited medication/treatments for chronic pain that patient cannot be withdrawn from prior to study treatment at Baseline and throughout the duration of the study
13. Any musculoskeletal condition that would impede measurement of efficacy at the target knee
14. Symptomatic OA of the contralateral knee or of either hip that is not responsive to paracetamol and requires other therapy
15. Systemic, or IA injection of corticosteroids in any joint within 3 months prior to Screening
16. Related hypersensitivities to avian proteins and/or any components of hyaluronan-based injection devices
17. Active infection, or history of an infection within the past 12 months, in the area to be injected
18. Any significant chronic skin disorder that could interfere with evaluation of the injection site
19. Heparin or anti-vitamin K (e.g., crystalline warfarin) anticoagulant therapy
20. Any known contraindication to paracetamol
21. Started the use of glucosamine, chondroitin sulfate, diacerhein, or avocado/soya extracts within 2 months prior to Screening
22. Uncontrolled diabetes mellitus, diabetic neuropathy, or infectious complications; end-stage hepatic or renal disease; or patients on immunosuppressive therapy
23. Current malignancy or treatment for malignancy within the past 5 years, except non-melanoma skin cancer
24. Active asthma that may require periodic treatment with systemic steroids during the study period (note: inhaled steroids for this condition are allowed)
25. Any significant medical condition (e.g., significant psychiatric or neurological disorders, active alcohol/drug abuse, etc.) or other factor (e.g., planned relocation)

that the Investigator feels would interfere with study evaluations and study participation

26. Used an investigational drug, device, or biologic within 3 months before Screening
27. Females who are pregnant, lactating or unwilling to use medically acceptable contraception, or women unwilling to perform a pregnancy test before administration of study treatment
28. Ongoing litigation for workers compensation for musculoskeletal injuries or disorders

<sup>a</sup>Anteroposterior view: weightbearing (extension or semi-flexion) + profile and a femoro-patellar view at 30° classical

### **7.3 Repeat Treatment Phase Inclusion Criteria**

Patients who complete the Week 26 assessments may be enrolled in the Repeat Treatment Phase of this study. **In order to receive Synvisc treatment during the Repeat Treatment Phase**, patients will be required to meet all of the following criteria:

1. Must continue to meet Screening Inclusion/Exclusion criteria
2. Must have no major safety concerns during the first course of treatment as assessed by the Investigator
3. Must have a WOMAC LK 3.1 A score of at least 1
4. Must, in the Investigator's clinical assessment, be a candidate for treatment
5. If female, must have a negative urine pregnancy test and continue to use a medically acceptable form 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.

### **7.4 Patient Withdrawal**

Patients are free to withdraw consent and discontinue study participation at any time and without prejudice to further treatment. In addition, a patient's participation in the study may be discontinued at the discretion of the Investigator at any time. Justifiable reasons for the Investigator to remove a patient from the study may include but are not limited to the following:

- The patient is uncooperative, including failure to appear at 1 or more study visits
- The patient develops a concurrent disease or condition that disqualifies him/her based on eligibility criteria
- The patient suffers an intolerable AE
- The Sponsor terminates the study

- Regulatory authority(ies) close the study

If a patient discontinues participation in the study, he or she will be contacted in order to obtain information about the reason(s) for discontinuation and collection of any potential AEs. Whenever possible the patient should return to the clinic for the final clinical assessments (Week 26). The Investigator will document on the Patient Completion/Discontinuation screen of the electronic Case Report Form (eCRF) the reason for discontinuation. Discontinued patients will be followed until all AEs resolve or until agreement is reached between the Sponsor and the Investigator that follow-up is no longer necessary.

## 8. CLINICAL TRIAL MATERIAL ADMINISTRATION

### 8.1 Treatments Administered

The investigational product being evaluated in this study is Synvisc (hylan G-F 20) which is a sterile, non-pyrogenic, elastoviscous fluid containing hylan polysaccharide hydrated in physiological saline. Hylan is a crosslinked derivative of hyaluronan, a natural polysaccharide (glycosaminoglycan) responsible for the elastoviscosity of synovial fluid. Synvisc (hylan G-F 20) consists of 2 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). Hylan A fluid constitutes 80% (per volume) and hylan B gel slurry 20% (per volume) of the final hylan G-F 20 fluid. Hylan B is produced by chemically crosslinking hylan molecules to form a molecular network ([Balazs, 1989, \*The Biology of Hyaluronan\*](#); [Balazs EA, 1993, \*Biotechnological Polymers\*](#); [Larsen, 1993, \*Journal of Biomedical Master Research\*](#)). It is a water-insoluble, viscoelastic hydrated gel. One millilitre of Synvisc contains 8 mg hylan polymer. The hydration fluid is buffered physiological sodium chloride solution (pH  $7.2 \pm 0.3$ ).

The placebo is PBS, which has the same formulation as the hydration fluid in Synvisc (buffered physiological sodium chloride solution [pH  $7.2 \pm 0.3$ ]).

#### 8.1.1 Injection Supplies

Below is a list of supplies for use during the injection procedure:

- Blinded patient kit containing either Synvisc or Placebo (PBS) (see [Table 8-1](#) for kit contents)
- Sterile gloves, mask
- Anaesthesia drape

#### 8.1.2 General Instructions

The same qualified professional ([Section 6.3](#)) must perform all injections for a given patient. The injection approach is left to the discretion of the Unblinded Injector and should, if medically possible, be the same each time for a given patient. For each injection procedure, the study staff should ensure the injection room is properly prepared prior to patient arrival. Preparation includes having the kit and all necessary supplies available, having a surgical drape in place to blind the patient, and ensuring the kit content is not visible to the patient.

### **8.1.3 Precautions for Joint Injection**

Prior to each injection, the Unblinded Injector must examine the injection site for any of the following signs or symptoms:

- Tense effusions
- Clinically significant redness or tenderness
- Any medically significant condition that could compromise patient safety or study integrity
- If any of these signs or symptoms is present, the Unblinded Injector must not carry out the procedure (see [Section 8.4](#) and [Section 9.3.8](#)).

Strict aseptic technique and universal precautions must be followed. NOTE: All injection procedure observations will be described in the injection manual and documented in the source material and the eCRF.

### **8.1.4 Injection Site Preparation**

The injection site should be disinfected carefully according to standard medical practice. Disinfectants containing quaternary ammonium salts are not permitted because hyaluronan can precipitate in their presence.

### **8.1.5 Anaesthetisation of the Injection Site**

Anaesthetisation of the injection site is not required. However, the Unblinded Injector may administer at his/her discretion a topical (e.g., ethyl chloride) or subcutaneous anaesthetic (e.g., lidocaine).

### **8.1.6 Arthrocentesis**

Arthrocentesis will be performed prior to every injection. Only 18- to 20-gauge needles are to be used for this study. Strict aseptic administration technique must be followed. The injection approach is left to the discretion of the Unblinded Injector. Gentle aspiration will be performed in an attempt to ascertain if the needle has been placed within the joint space. Any fluid or effusion will be withdrawn and the volume of the fluid/effusion will be recorded. Leaving the needle in the joint space, the syringe will be removed and replaced by a pre-filled syringe containing either Synvisc or Placebo (PBS). Care must be taken when manipulating the luer lock so as not to agitate or remove the needle or to incorrectly attach the next syringe (e.g., could cause leakage, etc.). Refer to [Section 8.1.7](#) for further administration instructions.

### **8.1.7 Injection of Synvisc or Placebo**

Remove the pre-filled 10-mL syringe from its packaging and use only if the packaging has not been opened or damaged. Notify Genzyme Clinical Pharmacy Research Services (CPRS) or your Study Monitor promptly if the packaging is not intact (see [Section 9.3.7](#) for Complaints Reporting). After the syringe has been removed from its packaging, immediately attach it to the 18- or 20-gauge needle that has been positioned in the joint; special care should be taken to ensure that the Unblinded Injector removes the tip cap from the syringe using aseptic technique before attaching to the needle.

Synvisc or Placebo (PBS) should NOT be injected extra-articularly, into the synovial tissues, into the capsule, or into the bursae. Each 10-mL syringe contains 6 mL of Synvisc or 6 mL of Placebo (PBS). Inject 6 mL into the target knee over 3 to 4 minutes, and then remove the needle and syringe.

If 6 mL of Synvisc or Placebo (PBS) cannot be injected, the reason must be documented. The total volume injected must be calculated and documented.

All procedures will be carefully documented in the patient notes and appropriate eCRF.

### **8.1.8 Postinjection Procedures**

After withdrawing the needle from the joint space, light pressure should be applied to the injection site, followed by application of a simple adhesive bandage. The patient should be encouraged to rest the injected joint for 24 hours. Patients are allowed to return to work that day but strenuous activity and driving for long distances in the 24 hours after each injection is not recommended. Typically there could be pain associated with the procedure. For postinjection pain management, it is recommended that patients rest and ice the injection site. All pharmacological and nonpharmacological treatments of postinjection pain must be captured on the eCRF.

All AEs and clinical findings prior, during, and immediately postinjection must be recorded. Patients experiencing pain and swelling at the target joint or any other AE will be instructed to contact the study staff.

## **8.2 Clinical Trial Material**

The dose volume regimen of Synvisc (6.0 mL) containing 48 mg of hylan polymer in buffered physiological sodium chloride solution (pH 7.2 ± 0.3) was selected for use in this study. An equal volume, 6.0 mL, of PBS will be utilised as the Placebo control.

### 8.2.1 Packaging and Labelling

Genzyme Europe B.V. CPRS will perform the secondary packaging and labelling of the clinical trial materials (CTM).

Label text will be prepared to meet the requirements of the participating countries, and the product will be described as Synvisc or Placebo to maintain the double-blind. All test devices will be labelled “For Investigational Use Only.” In addition, Patient Kits containing either Synvisc or Placebo will be packaged identically.

Genzyme Europe B.V. will pre-assign a Kit Code to each Patient Kit. This Kit Code will mask the identity of treatment assignment and provide a tracking mechanism for verification of kit assignment. Also, space will be provided on the label to write in the Patient Identification (ID) Number and Patient Initials.

**Table 8-1 Patient Kit Contents**

	<b>Day 0</b>
<u>Group 1</u> Arthrocentesis followed by a 6-mL IA injection of Synvisc on Day 0	One Synvisc 10-mL syringe One 20-gauge, 1.5-inch needle One 18-gauge, 1.5-inch needle One 10-mL syringe for arthrocentesis
<u>Group 2</u> Arthrocentesis followed by a 6-mL IA injection of Placebo (PBS) on Day 0	One Placebo 10-mL syringe One 20-gauge, 1.5-inch needle One 18-gauge, 1.5-inch needle One 10-mL syringe for arthrocentesis

### 8.2.2 Study Treatment Preparation

Both Synvisc and Placebo (PBS) are supplied in a pre-filled syringe. Therefore, no study treatment preparation is required for this clinical study protocol.

Each syringe is intended for single use. The contents of the syringe must be used immediately after the syringe has been removed from its packaging.

### 8.2.3 Patient Kit Storage

Kits with study product must be stored in a location with limited access, at a controlled temperature between 2°C and 30°C in the original packaging protected from light. The study product must not be frozen. Do not use any product if its package is opened or damaged.

The seal of the kit should not be broken until the treatment is prepared by unblinded study personnel.

#### **8.2.4 Clinical Trial Material Accountability**

The Investigator (or designee) will maintain accurate records of all CTM received, dispensed, and returned/destroyed at the clinical site.

Immediately after assigning a kit to a patient, patient ID number and initials are to be filled in on the kit. When the treatment has been given, the empty kit will be stored in a location with limited access until a Genzyme representative has performed the accountability check.

#### **8.3 Medications and Treatments**

Reasonable efforts will be made to determine all medications and treatments (pharmacological and non-pharmacological) received by the patient. Prior medications or treatments are defined as any medication or therapy taken by the patient within 1 month prior to Screening. A medication or treatment is considered concomitant if it is taken at any time after the Screening visit up to and including the day of the final study evaluation. Data on medications will include: name, dose, route, regimen, start date, stop date, and indication. Data on treatments will include: treatment, start date, stop date, and indication. At each study visit and during weekly phone calls, the patient will be asked about any additional medications or treatments or any changes in regimen or dosages since the last visit or contact. Indications for any new medications or treatments during the study period will be recorded as an AE.

Pain and OA medications will be discontinued for up to 21 days (depending on the medication half-life) before administering test material and throughout the study duration. The use of rescue medication and allowed analgesics (for medications with a half-life  $\leq 5$  hours) is permitted throughout the duration of the trial except for the 48 hours prior to study evaluations. At any visit, if the patient takes rescue medication (paracetamol) for knee pain or any other analgesic within that 48-hour period, then that visit must be rescheduled per the specified visit windows ([Table 9-3](#)) to allow for appropriate washout.

#### **8.4 Method of Assigning Patients to Treatment**

Each enrolled patient will ultimately receive a number comprising the following:

- A unique 2-digit Site number assigned by the Sponsor
- A 3-digit Screening number, corresponding to the order of the patient's enrolment in the study, and
- A 3-digit Randomisation number -- after Screening, this number will be "000." When the patient is randomised, the Randomisation number will correspond to the order of the patient's eligibility. If the patient does not qualify for randomisation, the last 3 digits will remain "000."
  - The number, when written out, will be in the following format:

Site Number	Screening Number			Randomisation Number			

After providing informed consent at Screening, each patient will be assigned the Site Number and the Screening Number, and all consenting patients will be documented in the patient Screening log. Each patient will complete all Screening procedures, and will be assessed to determine whether he/she fulfils the inclusion criteria and does not meet any of the exclusion criteria. If the patient qualifies to enter the study, the patient will be assigned a Randomisation Number.

Example: The second patient screened at Site 01, and the first to qualify for randomisation:

0	1	0	0	2	0	0	1
Site Number	Screening Number			Randomisation Number			

However, if the patient cannot be randomised due to screen failure, the patient will keep the number, “000” as the Randomisation Number:

Example: The first patient screened at Site 01 failed first screening attempt:

0	1	0	0	1	0	0	0
Site Number	Screening Number			Randomisation Number			

The site will be allowed 1 opportunity to re-screen each patient who fails to qualify for inclusion. A second screening attempt will be identified by changing the first digit of the Screening Number to “9.” Assuming that the patient qualifies to enter the study at the second screening attempt, the patient will then receive a Randomisation Number. The new, 8-digit number will be recorded in the enrolment and randomisation logs, the eCRF, and the database.

Example: The first patient screened at Site 01 failed first screening attempt, but passed the second, and was the second patient to be randomised at the site:

0	1	9	0	1	0	0	2
Site Number	Screening Number			Randomisation Number			

However, in the case of a second screen failure, the patient would keep the number 000 as the Randomisation Number:

Example: The first patient screened at Site 01 failed both screening attempts:

0	1	9	0	1	0	0	0
Site Number		Screening Number			Randomisation Number		

A patient who experiences a second screen failure can no longer be considered for entry into the study. Screen failure eCRFs will be monitored and included in the database. If a patient is re-screened (whether he/she is subsequently randomised or is again a screen failure) the eCRFs will be completed, monitored and included in the database.

### 8.5 Dose Selection

A pilot study (Genzyme Study SYN00502) and a re-treatment study (Genzyme Study SYN00602) were conducted to assess the safety and efficacy of alternate dosing regimens and re-treatment. Genzyme Study SYN00502 evaluated several combinations of higher single dose volumes (4 and 6 mL) and a reduced number of injections (1 or 2); subsequently, Genzyme Study SYN00602 evaluated a second cycle of the same treatment that a subset of patients had already received as participants in study SYN00502.

In Genzyme study SYN00502, all treatment regimens resulted in statistically significant improvement from Baseline to Week 24 in all endpoints for all treatment regimens. The 1 x 6-mL, 3 x 4-mL, and 3 x 2-mL treatment groups consistently showed the greatest mean improvement. In particular, the 1 x 6-mL treatment group was ranked either first or second in 5 of the 6 endpoints (Patient Pain, WOMAC A, WOMAC B, WOMAC C, Patient Global, and Physician Global).

Quantitatively, the 3 x 4-mL treatment group had the highest percentage of patients with treatment-related target knee AEs reported (30% of the patients), which was not unexpected in this group receiving the highest dose (12 mL, twice the current approved total dose). In the 1 x 6-mL treatment group, only 10% of patients had treatment-related target knee AEs; however, the 2 effusions observed in this study were both in this group.

Only a small number of patients were retreated with Synvisc in the SYN00602 extension study, limiting the interpretation of the data. However, neither of these studies raised any serious safety concerns related to Synvisc treatment at any of the studied dose regimens, nor was new safety concerns raised by re-treatment with these regimens.

### 8.6 Blinding and Randomisation

The clinical observer and patient will be blinded to the investigative study treatment received. The site personnel dispensing clinical supply and the unblinded injector will be instructed not

to reveal treatment regimens to the masked clinical observer to ensure that the blinding remains intact.

Upon fulfilling the eligibility criteria (as described in [Section 7.1](#) and [Section 7.2](#)) at Baseline (Day 0), each patient will receive a Randomisation Number. Site staff will then retrieve from storage the corresponding kit for the patient, based on the numbers written on the kit, according to instructions and training provided by the Sponsor. The Investigator (or designee) will write the patient's 8-digit identification number (see [Section 8.4](#)) and initials in the appropriate spaces on the label and in the accountability log, and will record the Kit Code and Patient Number in the study records. Tamper-evident seals on the kit cartons must not be removed until the day of administration, at which point only unblinded staff must open them.

## 9. EFFICACY AND SAFETY VARIABLES

### 9.1 Efficacy and Safety Measurements Assessed and Study Flowchart

This study will be conducted as outlined in the following sections. [Table 9-1](#) summarises the schedule of study events at each visit for patients enrolled in the Initial Phase of the study. Study visits will be based on calendar days from Baseline (Day 0). If the first injection does not occur on the same day as the Day 0 study visit (see [Section 8.4](#) regarding re-screens and [Table 9-3](#) regarding visit windows), subsequent study visits will be based on calendar days from the date of the first study intervention (injection) as shown in [Table 9-3](#). Re-screens and rescheduled visits must occur within the time windows specified in [Table 9-3](#).

[Table 9-2](#) summarises the schedule of study events for those patients who participate in the Repeat Treatment Phase of the study. Medication washout requirements are detailed in [Table 9-4](#).

**Table 9-1 Schedule of Study Events**

	Visit 1 (Screening)	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	- 21 days <sup>8</sup>	Day 0	Week 1 (± 4 days)	Week 4 (± 4 days)	Week 8 (± 7 days)	Week 12 (± 7 days)	Week 18 (± 7 days)	Week 26 <sup>9</sup> (± 7 days)
Written Informed Consent	X <sup>4</sup>							
Study Eligibility	X	X						X <sup>10</sup>
Demographics and Baseline Characteristics	X							
Height and Weight	X							
Vital Signs	X	X						X
Medical History	X							
Physical Examination	X							X
Target Knee Assessment	X	X	X	X	X	X	X	X
Pregnancy Test <sup>1</sup>		X <sup>1</sup>						X
Radiograph <sup>2</sup>	X <sup>2</sup>							
Prior Treatment and Medications <sup>3</sup>	X <sup>3</sup>							
Prohibited Medication Washout <sup>4</sup>	X <sup>4</sup>							
Rescue Medication Monitoring		X	X	X	X	X	X	X
WOMAC		X		X	X	X	X	X
PTGA		X		X	X	X	X	X
COGA <sup>5</sup>		X <sup>5</sup>		X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>
Randomisation <sup>6</sup>		X <sup>6</sup>						
Study Treatment		X						
AE Assessment and Recording	X	X	X	X	X	X	X	X
Concomitant Treatment and Medications <sup>7</sup>		X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>

1: Only if female

2: X-ray taken at Screening is only required if the patient has not had a valid X-ray taken within 3 months of study Screening.

3: Including start/stop dates plus dose, route, and regimen for all medications.

4: Patients must be consented prior to any study-specific procedures being performed including washout of any prohibited medications. All Baseline evaluations must occur prior to study material administration.

5: The blinded evaluator's COGA assessment must be performed following the patient's completion of questionnaires.

6: Patients will be randomised to 1 of 2 study treatment arms: Synvisc or Placebo.

7: Concomitant treatments are to be recorded at each site visit. The site will call each patient at 1-week intervals between visits, to collect data on concomitant medications.

8: Screening may occur up to 21 days prior to Day 0, to allow for medication washout.

9: Any patients withdrawing prematurely must complete all (Week 26) assessments/procedures at the final visit.

10: For patients participating in the Repeat Treatment Phase, study eligibility will be re-assessed at Week 26.

**Table 9-2 Schedule of Study Events –Repeat Treatment Phase**

	Repeat Visit 1	Repeat Visit 2	Repeat Visit 3
	Repeat Day 0 <sup>1</sup>	Repeat Week 1 (± 4 days)	Repeat Week 4 (± 4 days)
Study Eligibility	X		
Vital Signs	X <sup>5</sup>		X
Physical Examination	X <sup>5</sup>		X
Target Knee Assessment	X <sup>5</sup>	X	X
Pregnancy Test <sup>2</sup>	X <sup>5</sup>		X <sup>2</sup>
Rescue Medication Monitoring	X <sup>5</sup>	X	X
Study Treatment <sup>3</sup>	X <sup>3</sup>		
AE Assessment and Recording	X	X	X
Concomitant Treatment and Medications <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>

1: Repeat Day 0 will be synonymous with Week 26 of the treatment phase IF the patient qualifies for the Repeat Treatment Phase at the Week 26 visit.

2: Only if female

3: Study treatment must be administered by the same Unblinded Injector per patient within each study site throughout the trial. Study injection is only applicable for patients who qualified for and elected to receive study treatment administration.

4: Concomitant treatments are to be recorded at each site visit. The site will call each patient at 1-week intervals between visits, to collect data on concomitant medications.

5: These assessments are the ones performed for Visit 8 (Week 26) of the Initial Phase of the study. They will not be repeated as both Visit 8 (Week 26) and Repeat Visit 1 (Repeat Day 0) will be conducted on the same day.

**Table 9-3 Summary of Allowable Time Windows for Evaluations**

Visit	Study Week or Day <sup>1</sup>	Allowable Time Window (days) <sup>1</sup>	Repeat Treatment Phase		
			Repeat Visit	Repeat Week or Day	Allowable Time Window (days)
1	- 21 to 2 days	- 21	--	--	--
2	Day 0	--	1	Repeat Day 0	0
3	Week 1	± 4	2	Repeat Week 1	± 4
4	Week 4	± 4	3	Repeat Week 4	± 4
5	Week 8	± 7	--	--	--
6	Week 12	± 7	--	--	--
7	Week 18	± 7	--	--	--
8	Week 26	± 7	--	--	--

1: Screening may occur up to 21 days prior to Day 0, to allow for medication washout.

NOTE: Study visits will be based on calendar days from Baseline (Day 0). If the Day 0 injection does not occur on the same day as the Day 0 study visit, subsequent study visits will be based on calendar days from the date of the Day 0 injection.

**Table 9-4 Medication Washout Requirements**

Medication Not Allowed	Washout*
Prescription pain medications	Up to 21 days prior to test material administration
Prescription OA medications	
Paracetamol (other than rescue medication)	
Other analgesics and NSAIDs for knee OA pain	
Other pain and OA medications	

\*See appendices for examples of required washout periods.

## 9.2 Efficacy Assessments

All questionnaires provided to the patient will be in local language and must be completed only by the patient.

Patients are instructed to discontinue pain and OA medications with a half-life ≤ 5 hours by 48 hours prior to each study visit, so as not to interfere with any patient-rated efficacy assessments at any visit; if the patient takes paracetamol for target knee pain or any other analgesic within that 48-hour period, then his/her visit must be rescheduled, per the specified visit windows (see [Section 8.4](#) regarding re-screens and Table 9-3 regarding visit windows).

### 9.2.1 WOMAC LK Version 3.1

Visit	1	2	3	4	5	6	7	8
	Screen*	Day 0	Wk 1	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26
WOMAC LK 3.1		X		X	X	X	X	X

\*Screen = 2 to 21 days prior to Day 0

The WOMAC LK 3.1 questionnaire is a self-administered, health status measure used to probe symptoms of pain (WOMAC A), stiffness (WOMAC B), and physical function (WOMAC C) in patients with OA of the knee. The index consists of 24 questions (5 pain, 2 stiffness, and 17 physical function) (Bellamy, 1988, *J of Rheumatol*). All responses will be recorded directly on the electronic patient questionnaire (ePQ), and the ePQ will serve as source documentation.

The Likert scale uses a 5-point adjectival scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme) to capture the patient's response to each of the questions. The patient will be asked to check the box that indicates his/her amount of target joint pain, amount of stiffness, and degree of difficulty completing tasks within the past 48 hours.

### 9.2.2 Patient Global Assessment

Visit	1	2	3	4	5	6	7	8
	Screen*	Day 0	Wk 1	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26
PTGA		X		X	X	X	X	X

\*Screen = Up to 21 days prior to Day 0

The patient will give a global self-assessment (PTGA) of target knee OA condition using the Likert scale (0 = very well, 1 = well, 2 = fair, 3 = poor, 4 = very poor) to rate his/her OA. The patient's response will be recorded directly on the ePQ, and the ePQ will serve as the source document.

### 9.2.3 Clinical Observer Global Assessment

Visit	1	2	3	4	5	6	7	8
	Screen*	Day 0	Wk 1	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26
COGA		X		X	X	X	X	X

\*Screen = Up to 21 days prior to Day 0

The blinded evaluator will give a global assessment (COGA) of the target knee OA using the Likert scale (0 = very well, 1 = well, 2 = fair, 3 = poor, 4 = very poor) to rate the patient's target knee OA. The same blinded evaluator will complete this assessment for all patients at

a site, and all COGAs must be completed after the patient self-assessments. COGA responses will be entered into the eCRF.

### 9.3 Safety Assessments

#### 9.3.1 Medical History and Demographics

Visit	1	2	3	4	5	6	7	8
	Screen*	Day 0	Wk 1	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26
Medical History and Demographics	X							

\*Screen = Up to 21 days prior to Day 0

A medical history must be obtained at Screening (up to 21 days prior to Day 0). Specific information will be recorded on the eCRF relating to any prior or existing medical conditions/surgical procedures involving the following categories: Infectious Diseases, Allergic, Metabolic/Endocrine/Nutritional, Haematopoietic, Musculoskeletal, Dermatological, Head, Ears, Eyes, Nose, and Throat (HEENT), Breasts, Respiratory, Cardiovascular, Gastrointestinal/Hepatic, Genitourinary/Renal, Neurological, and Psychiatric/Psychosocial.

The patient will be asked to provide a relevant medical history with specific dates. Those conditions and/or procedures reported will be compared to the inclusion and exclusion criteria for the study. Specific attention will be paid to the patient's previous history with respect to exclusionary conditions, procedures, and surgeries.

Demographic data, height, and weight will also be recorded at the Screening visit.

### 9.3.2 Vital Signs

Visit	1	2	3	4	5	6	7	8
	Screen*	Day 0	Wk 1	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26
Vital Signs	X	X						X

\*Screen = Up to 21 days prior to Day 0

Visit	Repeat Visit 1	Repeat Visit 2	Repeat Visit 3
	Repeat Day 0**	Repeat Week 1	Repeat Week 4
Vital Signs	X		X

\*\* Repeat Day 0 will be synonymous with Week 26 of the treatment phase IF the patient qualifies for the Repeat Treatment Phase at the Week 26 visit.

Vital signs (blood pressure, heart rate, and temperature) will be measured at Screening (Up to 21 days prior to Day 0), Baseline (Day 0), and Week 26. Any clinically significant abnormal findings will be recorded on the AE page of the eCRF.

If a clinically significant deterioration is noted, the changes will be documented as AEs on the eCRF. Clinical significance is defined as any variation in physical findings that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to its baseline status or until agreement is reached between the Investigator and Sponsor.

### 9.3.3 Physical Examination

Visit	1	2	3	4	5	6	7	8
	Screen*	Day 0	Wk 1	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26
Physical Examination	X							X

\*Screen = Up to 21 days prior to Day 0

Visit	Repeat Visit 1	Repeat Visit 2	Repeat Visit 3
	Repeat Day 0**	Repeat Week 1	Repeat Week 4
Physical Examination	X		X

\*\* Repeat Day 0 will be synonymous with Week 26 of the treatment phase IF the patient qualifies for the Repeat Treatment Phase at the Week 26 visit.

A physical examination will be conducted at Screening (up to 21 days prior to Day 0) and Week 26 or the final study visit. Any abnormal findings will be recorded on the eCRF.

If a clinically significant deterioration is noted, the changes will be documented as AEs on the eCRF. Clinical significance is defined as any variation in physical findings that has

medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to its baseline status or until agreement is reached between the Investigator and Sponsor.

### 9.3.4 Target Knee Assessment

Visit	1	2	3	4	5	6	7	8
	Screen*	Day 0	Wk 1	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26
Target Knee Assessment	X	X	X	X	X	X	X	X

\*Screen = Up to 21 days prior to Day 0

Visit	Repeat Visit 1	Repeat Visit 2	Repeat Visit 3
	Repeat Day 0**	Repeat Week 1	Repeat Week 4
Target Knee Assessment	X	X	X

\*\* Repeat Day 0 will be synonymous with Week 26 of the treatment phase IF the patient qualifies for the Repeat Treatment Phase at the Week 26 visit.

A target knee assessment will be performed at each study visit. If a clinically significant deterioration is noted, the changes will be recorded as AEs on the eCRF. Any variation in target knee assessment findings that has medical relevance or may result in an alteration in medical care should be considered clinically significant. The Investigator will continue to monitor the patient until the parameter returns to its baseline status or until agreement is reached between the Investigator and Sponsor.

### 9.3.5 Pregnancy Test

Visit	1	2	3	4	5	6	7	8
	Screen*	Day 0 (Baseline)	Wk 1	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26
Pregnancy Test		X						X

\*Screen = Up to 21 days prior to Day 0

Visit	Repeat Visit 1	Repeat Visit 2	Repeat Visit 3
	Repeat Day 0**	Repeat Week 1	Repeat Week 4
Pregnancy Test***	X		X

\*\* Repeat Day 0 will be synonymous with Week 26 of the treatment phase IF the patient qualifies for the Repeat Treatment Phase at the Week 26 visit.

\*\*\* Only if female

Females will undergo a urine pregnancy test at Baseline and Week 26. Patients will be carefully screened to ensure that all women of childbearing potential have used a medically acceptable form of contraception for at least 1 month prior to Screening and will continue use

for the duration of the study period. Women who cannot comply will not be enrolled in the study.

Women of nonchildbearing potential must confirm that they are surgically sterile, or have been postmenopausal for at least 1 year prior to study treatment. This information will be recorded on the Medical History page of the eCRF.

At Repeat Week 4, women must undergo another urine pregnancy test.

### 9.3.6 Adverse Events

Visit	1	2	3	4	5	6	7	8
	Screen*	Day 0	Wk 1	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26
AE Assessment and Recording	X	X	X	X	X	X	X	X

\*Screen = Up to 21 days prior to Day 0

Visit	Repeat Visit 1	Repeat Visit 2	Repeat Visit 3
	Repeat Day 0**	Repeat Week 1	Repeat Week 4
AE Assessment and Recording	X	X	X

\*\* Repeat Day 0 will be synonymous with Week 26 of the treatment phase IF the patient qualifies for the Repeat Treatment Phase at the Week 26 visit.

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical or medical device product and which does not necessarily have a causal relationship with this treatment. AEs therefore include any undesirable physical, psychological or behavioural effect experienced by a patient or subject during their participation in this investigational study, in conjunction with the viscosupplementation with Synvisc, whether or not considered related to Synvisc. AEs experienced by the patient should be reported from the time of signing the informed consent until completion of the study. See [Section 9.3.6.3](#) for additional details on AE collection.

Local symptoms in the treated knee following IA injection may be similar to the symptoms occurring during the natural course of OA (e.g. pain, swelling, effusion). Therefore, such local symptoms in the treated knee subsequent to the IA procedure only will be classified as AEs when the local symptoms are worse than those observed at Baseline.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient or subject and/or observed by the Investigator or medical staff
- Laboratory abnormalities of clinical significance

Disease signs, symptoms and/or laboratory abnormalities that are present after treatment but already existed before the use of Synvisc will not be considered AEs unless:

- They recur after the patient had recovered from the pre-existing condition.
- They represent a clinically significant exacerbation in intensity or frequency in the opinion of the Investigator.

All disease signs and symptoms experienced by the patient will be recorded on the eCRF from the time of signing of the informed consent onwards until completion of the final study visit.

If clinically significant worsening of the subjects' physical condition from Screening is noted, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance is defined as any variation in signs, symptoms, or testing that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the assessment returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

#### **9.3.6.1 Serious Adverse Events**

A SAE is defined as any AE, irrespective of a possible relationship to the study device that results in any of the following outcomes:

- Death
- Life-threatening event
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Congenital anomaly
- An important medical event (for definition see below)

The following explanations apply to the above listed definitions:

Life-threatening event: Any AE that places the patient, in the view of the Investigator, at immediate risk of death from the AE as it occurred; i.e., does not include an AE that had it occurred in a more severe form, might have caused death.

Requires inpatient hospitalisation or prolongation of existing hospitalisation: Any AE that requires an overnight stay in a hospital or requires prolongation of an existing hospitalisation should be classified as serious.

Results in persistent or significant disability/incapacity: The AE that resulted in a substantial disruption of a person's ability to conduct normal life functions.

Congenital anomaly: Any physiological or physical defect observed in a child born from a mother who participated in the current study and who became pregnant during the course of this study (see below).

Important medical events that may jeopardise the patient or subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above: An AE that does not itself result in death, a life-threatening situation, or does not require hospitalisation may be considered a SAE when, based upon appropriate medical judgment, it may jeopardise the patient or subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above. See [Section 9.3.6.6](#) for additional details on AE collection.

### **9.3.6.2 Pregnancy**

All pregnancies occurring during the study are to be reported in the same timeframe as a SAE. All reports of pregnancy must be followed for information regarding the course of the pregnancy and delivery, as well as the condition of the infant. This should be reported to Genzyme Europe BV in a timely manner (see [Section 9.3.6.6](#)).

### **9.3.6.3 Adverse Events Description**

#### **9.3.6.3.1 Relationship of Adverse Events**

The Investigator will assess relationship between the AE and Synvisc according to the following definitions:

- Unrelated: There is no relationship between the AE and the use of the investigational device. This may include but is not limited to the incident being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the patient experienced.
- Remote/unlikely: There is no clear relationship between the AE and the use of the device under investigation and it is unlikely that there is some relationship. Genzyme will evaluate "Remote" as not related to the device with regards to reporting to the authorities
- Possible: There is no clear relationship between the AE and the use of the study device; however, one cannot definitely conclude that there is no relationship.
- Probable: While a clear relationship to the device under investigation cannot be established, the AE is associated with an expected AE or there is no other medical condition or intervention, which could explain the occurrence of such an event.
- Definite: The relationship of the AE and the use of the study device can definitely established.

#### 9.3.6.4 Severity of Adverse Events

The Investigator will be asked to assess the severity of the AE using the following categories: Mild, Moderate and Severe. This assessment is subjective and the Investigator should use medical judgment to compare the reported AE to similar type events observed in clinical practice. Below are listed guidelines for severity assessment:

- Mild: Symptom(s) that is barely noticeable to the subject/patient or does not make the subject/patient uncomfortable. The AE does not influence performance or functioning. Treatment ordinarily is not needed for relief of symptom(s).
- Moderate: Symptom(s) of a sufficient severity to make the subject/patient uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
- Severe: Symptom(s) of a sufficient severity to cause the subject/patient severe discomfort. Severity may cause cessation of treatment with the study drug. Treatment for symptom(s) may be given.

N.B., Severity is not equivalent to seriousness. The term "severe" should describe the intensity of the event (e.g., mild, moderate, severe headache) whereas the seriousness of the event is based on the subject/event outcome on action criteria usually associated with events posing a threat to the subjects' life or well-being (ICH Topic E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" CPMP/ICH/377/95, November 1994).

#### 9.3.6.5 Outcome of Adverse Events

The Investigator will be asked to indicate the outcome of the AE using the following categories: Recovered without sequelae, Recovered with sequelae, Not yet recovered, Unknown, or Other. This assessment is subjective and the Investigator should use medical judgment to compare the reported AE to similar type events observed in clinical practice. Below are the applicable guidelines for outcome assessment:

- Recovered without sequelae: The AE has resolved without residual symptoms.
- Recovered with sequelae: The AE has resolved, however, residual consequences will persist.
- Not yet recovered: The AE continues.
- Unknown: The outcome of the AE cannot be determined.
- Other: All other outcomes not described above. The Investigator will be requested to explain this classification.

### 9.3.6.6 Adverse Event and Serious Adverse Event Reporting

All AEs occurring during the course of the clinical trial will be documented and reported to the sponsor by the Investigator according to ICH-GCP, EN540, Council Directive 93/42/EEC, Council Directive 2001/20/EC (if applicable), and the specific definitions and instructions detailed in the Standard Operating Procedures (Standard Operating Procedures of Genzyme Europe BV).

The necessity and time requirements for reporting of AEs to the Sponsor or designee and/or regulatory agencies are as follows:

All (S)AEs will be recorded on the eCRF, with a full description including the nature, date and time of onset and resolution, determination of seriousness, frequency, severity, corrective treatment, outcome, and relationship to Synvisc.

All SAEs must be reported **within 24 hours** of the Investigator's first knowledge of the event, irrespective of a potential relationship to the Synvisc. Communications are to be directed to the Genzyme Europe BV Pharmacovigilance Department:

Phone: +31 35 699 1449 / +31 35 699 1299 (night/weekend).
Fax: +31 35 694 8756.

For all SAEs, **within 48 hours** of the Investigator's first knowledge of the event, the following documents must be sent to the Genzyme Europe BV Pharmacovigilance Department by fax:

- The completed Investigational Device SAE Report Form containing a detailed written description of the event;
- Additional anonymised supporting reports (e.g., discharge letters, autopsy reports).

The original completed Investigational Device SAE Report Form must be sent by mail to the Genzyme Europe BV Pharmacovigilance Department as soon as possible. A copy will be retained at site.

Contact person at Genzyme Europe BV:

Ivar Dijkstra, PhD Genzyme Europe BV, Pharmacovigilance Gooimeer 10 1411 DD Naarden The Netherlands Phone: +31 35 699 1449 (weekdays) Phone: +31 35 699 1299 (nights/weekends) Fax: +31 35 694 8756
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After the study is completed, if the Investigator or study staff becomes aware of a possibly related SAE, this event and any known details must be reported promptly to Genzyme Europe BV, Pharmacovigilance Department (see details provided above).

The Sponsor will report Serious Adverse Device Reactions to the appropriate regulatory authorities in accordance with the applicable European and national regulations. Where required, the Investigator or the sponsor should notify the Independent Ethics Committee (IEC).

#### **9.3.6.7 Serious Adverse Event Stopping Rule**

In case unexpected SAEs occur, which have not been identified in nature, severity or frequency in this protocol or the Investigator Brochure and, which are thought to be possibly related to Synvisc and are considered to be a health risk for all participating subjects, Genzyme may decide in consultation with the participating Investigators to postpone treatment of newly included patients and to discontinue the treatment of included subjects until the Investigators and Genzyme have thoroughly investigated the event(s) and conclude that continuation of the clinical trial is justified.

#### **9.3.6.8 Adverse Event Follow-up**

All AEs labeled "not yet recovered" will be followed by Genzyme in consultation with the Investigator. The duration of the follow-up will depend on seriousness and potential relationship to the investigational device as outlined below:

- Genzyme will complete follow-up on all "not yet recovered" non-serious AEs in consultation with the Investigator during completion of the final study visit, unless the Investigator determines from a medical perspective that follow-up is required for a longer period.
- Genzyme will continue follow-up on all "not yet recovered" SAEs in consultation with the Investigator until the subject has recovered, or until stabilisation of the condition has been achieved and the Investigator determines that follow-up is no longer required from a medical perspective.

### 9.3.7 Product Handling and Complaints Reporting

Investigators will promptly notify a Genzyme CPRS representative of any complaint concerning the CTM. A complaint for a clinical product is defined as the following: dissatisfaction regarding the identity, quality, durability, reliability, or performance of the product.

<b>Clinical Pharmacy Research Services (CPRS) Genzyme Europe B.V.</b>
Carmen Salazar, PhD Clinical Pharmacist
Phone +31 35 699 8687 (weekdays) Fax +31 35 699 1403 Or Phone +31 35 699 1200 (nights/weekends)

### 9.3.8 Summary of Risks

#### 9.3.8.1 Risks Associated With The Use of Synvisc

Synvisc contains small amounts of avian protein and should not be used in patients with related hypersensitivities.

Transient pain, and/or swelling, and/or effusion in the injected joint may occur after IA injections of Synvisc. In some cases the effusion may be large and can cause pronounced pain. It is important to remove and to analyse the fluid to rule out infection or crystalline arthropathies. These reactions generally abate within a few days. Clinical benefit from the treatment may still be apparent after such reactions. IA infections did not occur in any of the clinical trials and have been reported only rarely during clinical use of Synvisc.

In controlled clinical trials, there were no statistically significant differences in the number or types of AEs between the group of patients that received Synvisc and the group that received control treatments. Postmarketing experience has identified the following events to occur rarely with Synvisc administration: rash, hives, itching, fever, nausea, headache, dizziness, chills, muscle cramps, paresthesia, peripheral oedema, malaise, respiratory difficulties, flushing and facial swelling.

#### 9.3.8.2 Risks Associated With The Injection Procedure

Certain risks are specifically associated with IA insertion of a needle into the joint, irrespective of the implanted device material. These risks have been reported with regard to IA injection of corticosteroids. Such risks include bleeding, infection, and joint injury, all

rare. AEs, generally in the area of the injection, have occurred following extra-articular injection of Synvisc.

Various injection techniques can be employed for the IA injection. The risks associated with IA injections can be minimised by ensuring accurate needle placement into the IA joint space. Additionally, strict aseptic procedures should be maintained during the procedure to reduce the risk of infection.

## **10. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT**

### **10.1 Source Documents**

Original documents, data, and records include hospital records, clinical and office charts, laboratory notes/reports, memoranda, patients' evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions certified after verification as being accurate copies, source document worksheets (i.e., for study visits, including the interim phone call worksheets), and X-rays are considered source documents. Medical histories and narrative statements relating to the subject's progress (i.e., source documents) will be maintained during the trial and for a period of 15 years after completion of the study (See [Section 12.3.3](#)). The Investigator must provide direct access to the source documents to Genzyme or its representative.

All data captured for this study are to be recorded in the patient's notes first and then entered in the eCRF, except for the items listed below. These are considered source documents, and will be completed by the patient and recorded directly into an ePQ:

- WOMAC LK 3.1
- PTGA

### **10.2 Recording of Data**

The Investigator will be responsible for retaining all records pertaining to the trial for a period of 15 years, and in accordance with local regulatory and legal requirements.

Clinical data will be entered using electronic data capture technology from eTrials Incorporated. All data captured electronically will be provided on a CD-ROM at the end of the study in pdf format.

All required data will be recorded in the eCRF or ePQ. All missing data will be explained. Any changes made to the data after initial entry will be captured in an electronic audit trail.

### **10.3 Data Quality Assurance**

Upon completion of data entry, the data will be reviewed by a clinical monitor from Genzyme or a representative of the Sponsor to ensure acceptable accuracy and completeness. The database will undergo further quality assurance (QA) by Genzyme Data Management. If necessary, the study site will be contacted for corrections and/or clarifications. Any additional data captured electronically (e.g., laboratory data) will be electronically transferred to the database.

#### **10.4 Data Management**

Genzyme or a representative of the Sponsor will be responsible for:

- Database creation and validation
- eCRF review and data validation

Prior to finalising and locking the database, all decisions concerning the inclusion or exclusion of data from the analysis for each patient will be determined by appropriate clinical and statistical personnel. Any and all exclusions related to either safety or efficacy will be documented in patient listings.

## 11. STATISTICAL METHODS AND PLANNED ANALYSES

Genzyme or a representative of the Sponsor will be responsible for the production of the following items:

- Data listings and summary tables
- Statistical analysis
- Combined clinical and statistical study report

All eCRF data, as well as any outcomes derived from the data, will be summarised in detailed data listings. Patient data listings will be presented for all patients enrolled into the study.

### 11.1 Efficacy Objectives

#### 11.1.1 Primary Efficacy Objective

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

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

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

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

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

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

The criterion for success for this study is defined as a statistically significant overall difference between the Synvisc treatment group and the Placebo (PBS) group at the 5% significance level. It is anticipated that the differences in the change from Baseline (WOMAC LK 3.1 A) between the Synvisc treatment groups and the Placebo (PBS) group at the post-3-month study visits will meet the criteria for clinically meaningful differences that was noted in the literature by Ehrich, et al. (Ehrich, 2000, *J of Rheumatol.*). Statistical inference will be based on a repeated measures analysis.

### 11.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives of this study are:

- To analyse the differences between the WOMAC A subscore from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group
- To analyse the differences between the WOMAC A1 subscore over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group
- To analyse the differences between the WOMAC C subscore over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group
- To analyse the differences between the PTGA over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group
- To analyse the differences between the COGA over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group
- To analyse the differences between the percentages of positive responders to treatment for symptomatic primary OA of the knee over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group (where response is defined with the OMERACT OARSI set of responder criteria [[Pham, 2003, \*J of Rheumatol\*](#); [Pham, 2004, \*Osteoarthritis Cartilage\*](#)])

### 11.1.3 Tertiary Efficacy Objectives

The tertiary efficacy objectives of this study are as follows:

- To analyse the differences between the Total WOMAC score over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group
- To analyse the differences between the WOMAC B subscore over 26 weeks and from Baseline to the Week 26 assessment in the Synvisc treatment group and the Placebo (PBS) group
- To analyse the differences between the average daily consumption of paracetamol (grams) over 26 weeks in the Synvisc treatment group and the Placebo (PBS) group

## 11.2 Safety Endpoints

Safety will be determined using the incidence of treatment-emergent AEs, vital signs, and physical examination findings. AEs will be categorised using a standardised coding dictionary (e.g., MedDRA).

### 11.3 Analysis Methods

#### 11.3.1 Demographics and Baseline Characteristics

Baseline demographic and background variables will be summarised by treatment group and overall. For categorical variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics including sample size, mean, median, standard deviation, minimum, and maximum, will be presented.

#### 11.3.2 Patient Accountability

All patients enrolled will be included in a summary of patient accountability for this study. The frequency and percentages of patients enrolled, presenting at each visit, discontinuing before study completion (including reason for discontinuation), and completing the study will be presented.

#### 11.3.3 Efficacy Analyses

##### 11.3.3.1 Primary Efficacy Analysis

The primary efficacy analysis will be performed on the ITT Population, which will include all patients randomised, and will be based on a repeated measures model that will be used to test for differences in treatment efficacy, as quantified by the WOMAC LK 3.1 A subscore over 26 weeks between Synvisc and PBS. The test of treatment efficacy will be constructed using least-square mean estimates (linear combinations of the estimated regression parameters). The description of the repeated measures model that will be fit to the data and the construction of the test statistic that will be used for the primary efficacy objective follows:

Let  $\mathbf{y}_i$  be a  $n_i \times 1$  vector of pain measurement observations (WOMAC LK 3.1 A subscore change from Baseline) for the  $i$ th subject where  $n_i$  is the number of observations for the  $i$ th subject. The repeated measures model assumes that the WOMAC A subscore can be expressed as a linear function of treatment, time, treatment-by-time interaction, Baseline level of pain and clinical site effects:

$$\mathbf{y}_i = \mathbf{X}_i \boldsymbol{\beta} + \mathbf{e}_i$$

where  $\boldsymbol{\beta}$  is a  $p \times 1$  vector of regression parameters,  $\mathbf{X}_i$  is the associated  $n_i \times p$  design matrix and  $\mathbf{e}_i$  is the error vector with  $E(\mathbf{e}_i) = \mathbf{0}$  and  $Var(\mathbf{e}_i) = \sigma_e^2 \mathbf{V}$  ( $\mathbf{V}$  is an unstructured variance-covariance matrix that must be estimated). The parameter vector  $\boldsymbol{\beta}$  can be partitioned as  $\boldsymbol{\beta}^T = (\mu | \boldsymbol{\alpha} | \boldsymbol{\tau} | \boldsymbol{\gamma} | \boldsymbol{\theta})^T$  where  $\mu$  is the overall mean,  $\boldsymbol{\alpha} = \{\alpha_k\}_{(1 \times 1)}$  is the subvector of treatment effects,  $\boldsymbol{\tau} = \{\tau_l\}_{(5 \times 1)}$  is the subvector of post-Baseline visit effects,  $\boldsymbol{\gamma} = \{\gamma_{kl}\}_{(5 \times 1)}$  is the subvector of treatment-by-visit interaction effects and  $\boldsymbol{\theta}$  is the subvector of covariate regression parameters such as clinical center and Baseline measure of pain.

The primary efficacy objective is to compare the mean difference in the change from Baseline measure of pain relief between Synvisc and PBS over all post-Baseline study visits. This comparison is a function of the least-square mean estimates of the treatment-study visit combinations. The least-square mean difference between the 26-week WOMAC A change from Baseline in the Synvisc group and the Placebo (PBS) group is expressed as  $\delta_{26} = (\hat{\alpha}_2 - \hat{\alpha}_1) + (\hat{\gamma}_{2,26} - \hat{\gamma}_{1,26})$ , where the ‘^’ symbol denotes an estimated parameter and  $\hat{\gamma}_{k,26}$  is the estimated interaction between the Week 26 of follow-up and treatment k. The average difference over all of the study visits is estimated as

$$\hat{\delta}_{over} = \frac{1}{5} \sum_k \delta_k = (\hat{\alpha}_2 - \hat{\alpha}_1) + \frac{1}{5} \sum_k (\hat{\gamma}_{2k} - \hat{\gamma}_{1k}),$$

where the summation is over all 5 of the post-Baseline visits.

The estimate  $\hat{\delta}_{over}$  is the basis for the test of the  $H_0$  null hypothesis. It should be noted that the inclusion of additional covariates (e.g., Baseline measure of pain) does not alter the functional form of the  $\delta_{over}$  estimator. In addition, while the individual parameters that comprise  $\delta_{over}$  are not estimable, the linear functions are. The hypothesis tests are carried out using an estimate of  $\text{var}(\hat{\delta}_{over})$  and computing the respective Wald statistics.

The statistical inference regarding the  $\delta_{over}$  parameter in the repeated measures model can be closely approximated using 2-sample t-tests or ANCOVA. To test  $H_0$  using these methods, the mean change from Baseline across study visits for each patient is computed and used as treatment-specific observations in a 2-sample t-test or as the dependent variable in an ANCOVA model.

For the analysis based on repeated-measures models, missing data will be imputed using LOCF. The robustness of the results to the LOCF method will be assessed in a sensitivity analysis that may include multiple imputation.

The primary efficacy analysis may be repeated on the Per-Protocol Population, which will exclude all patients with major protocol violations.

### **11.3.3.2 Secondary and Tertiary Efficacy Analyses**

As with the primary efficacy analysis, the secondary and tertiary efficacy analyses will be performed on the ITT Population.

For the analysis of the WOMAC A, WOMAC B, WOMAC C, Total WOMAC, PTGA, and COGA, a repeated-measures linear model will be used as described in the primary efficacy analysis ([Section 11.3.3.1](#)).

For the analysis of the percentages of positive responders, logistic regression modelling and GEE modelling will be used. Using the Baseline and follow-up data, patients will be defined

as responders or non-responders based on the OMERACT-OARSI set of criteria (Pham, 2003, *Journal of Rheumatology*; Pham, 2004, *Osteoarthritis Cartilag*). The binary classification (response, no response) will be used in the logistic regression modelling, which will include covariates for treatment group assignment and relevant baseline covariates, to analyse the differences between the percentages of positive responders from Baseline to each post-Baseline assessment in the Synvisc treatment group and the Placebo (PBS) group. A Wald test based on the estimated regression parameter for treatment group assignment will provide the basis for the hypothesis testing. Differences in the percentages of positive responders over 26 weeks in the Synvisc treatment group and the Placebo (PBS) group will be analysed with GEE. For each post-Baseline study visit, patients will be defined as responders or non-responders based on the OMERACT-OARSI set of criteria. These repeated binary outcomes (responders/non-responder) will be modelled with GEE and a Wald test based on the estimated regression parameter for treatment group assignment will provide the basis for hypothesis testing for this secondary efficacy objective. 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 efficacy data imputed using the LOCF method.

The overall 26-week difference and the change from Baseline to Week 26 for the WOMAC A1 will be analysed using 2-sample t-tests. While the other measures used for the efficacy analyses are averages of scores that comprise the respective WOMAC subsections, the WOMAC A1 is 1 question measured on the Likert scale and therefore does not exhibit the requisite properties for a repeated measures analysis. However, treatment-specific means of changes from Baseline at Week 26 or overall changes from Baseline are anticipated to meet the distributional requirements for the t-test. The analysis of paracetamol usage will also be based on a 2-sample t-test.

Figures illustrating the longitudinal response profiles of the Synvisc and Placebo (PBS) groups for the efficacy variables will be provided. Tables summarizing the efficacy variables including the sample size, mean, median, SD, and range, will be presented.

#### **11.3.4 Safety Analysis**

The safety analyses will be performed on the Safety Population defined as all patients who undergo the first injection. Treatment-emergent AEs will be summarised by treatment group and categorised by severity and relationship to the study procedures. Treatment-emergent AEs will be summarized both including and excluding AEs generated from deteriorations in the target knee assessment (if any). If a patient has more than 1 occurrence of the same AE, he/she will be 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, will be indicated in cases of multiple occurrences of the same AE. Target knee AEs also will be summarized separately. All AEs will be presented in a listing. Additionally listings of SAEs and AEs leading to discontinuation will be generated.

Vital signs and physical examination findings will be tabulated. Concomitant medications and treatments will be categorised using a standardised coding dictionary (e.g., MedDRA, WHO-drug) and summarised.

For the Repeat Treatment Phase of the study, all treatment-emergent AEs will be summarised.

#### **11.4 Power and Sample Size**

Approximately 250 patients with symptomatic primary OA of the knee will be randomised. Sample size estimation is based on using the mean difference in the WOMAC LK 3.1 A change from Baseline in the primary efficacy analysis. The following assumptions were made to compute the sample size:

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

With these assumptions, a sample size of approximately 250 (125 patients per treatment arm) provides over 80% power to detect an overall difference of 0.297 (WOMAC LK 3.1 A) between the Synvisc treatment group and the Placebo (PBS) group over the course of 26 weeks. The assumption of a common SD of 0.725 and overall difference of 0.297 were based on the results of Genzyme/Wyeth Study Number 901 (Caborn, 2004, *J of Rheumatol*). The overall difference of 0.297 is a function of the progressive effectiveness of viscosupplementation. The differences between viscosupplementation and PBS are anticipated to increase to clinically meaningful extents (greater than 0.40) after approximately 3 months. A clinically meaningful difference of between 0.40 and 0.50 was noted in the literature by Ehrich, et al. (Ehrich, 2000, *J of Rheumatology*).

## **11.5 Other Considerations**

Clinical data will be captured and data management performed using electronic data capture (EDC) technology from eTrials<sup>®</sup>.

Statistical analysis will be performed on validated systems including Statistical Analysis Systems (SAS<sup>®</sup>) version 8.2.

### **11.5.1 Significance Levels**

The type I error rate will be set at the 5% significance level for the primary efficacy analysis. All secondary and tertiary efficacy analyses will be performed at the 5% significance level. No adjustment will be made for multiple comparisons.

### **11.5.2 Missing or Invalid Data**

For the efficacy analysis based on repeated-measures models, missing data will be imputed using LOCF. The robustness of the results to the LOCF method will be assessed in a sensitivity analysis that may include multiple imputation.

For the efficacy analysis based percentages of positive responders, patients who discontinue the study due to target knee AEs or lack of efficacy and, subsequently, have missing efficacy data will be classified as non-responders. Patients who discontinue the study for other reasons will have efficacy data imputed using the LOCF.

No replacement on any missing or invalid data will be made for the safety analyses.

### **11.5.3 Interim Safety Analysis**

An interim safety analysis may be performed by Genzyme's Biomedical Operations group when 50% of patients have completed their Week 8 study visit. The interim analysis will consist of summaries of treatment-emergent AEs by treatment group and categorised by severity and relationship to the study procedures. All AEs will be presented in a listing. The blind will be broken at the time of the interim safety analysis; however, only Genzyme personnel not involved in this clinical trial will be involved in this analysis.

## **12. SPECIAL REQUIREMENTS AND PROCEDURES**

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of GCP guidelines and the 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 Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

### **12.1 Institutional and Ethical Review**

This protocol and patient informed consent form must be reviewed and approved by the appropriate Independent Ethics Committee (IEC) in compliance with the requirements of the International Conference on Harmonisation, before enrolment of patients. Genzyme must receive the letter or certificate of approval from the IEC before delivery of clinical supplies.

### **12.2 Changes to the Conduct of the Study or Protocol**

No change in the study procedures shall be effected without the mutual agreement of the Investigator and Genzyme. All changes must be documented by signed protocol amendments. If changes to the design of the study are made, the amendment must be submitted to, and approved by, the IEC, signed by the Investigator, and returned to Genzyme for submission to the appropriate regulatory agencies.

### **12.3 Investigator's Responsibilities**

#### **12.3.1 Patient Informed Consent**

Appropriate patients who present to a participating physician will be offered the opportunity to participate. Patients must be provided with sufficient information and be allowed adequate time in which to decide whether they will participate, e.g., patients must be provided with sufficient time to read the Informed Consent Form, ask any questions of the Investigator and/or designee, and have all questions answered to his/her satisfaction. A recruitment log will be maintained at each site of all patients who present to the site, including those who are not enrolled into the study. The log will document the reason the patient was not included. Written informed consent is required prior to enrolment in the study. It is the responsibility of the Investigator to obtain such consent. Investigators must comply, as applicable, with GCP guidelines 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) when developing the patient informed consent.

The Investigator must furnish Genzyme with a photocopy of the proposed consent form prior to submitting to the EC so that Genzyme may ensure that all appropriate elements are

incorporated into the document. Upon approval by the EC, the Investigator must furnish the letter stating that formal EC approval has been granted by the institution (referencing the version date of the informed consent), prior to the release of clinical supplies.

### **12.3.2 Case Report Forms**

All data will be obtained using EDC. Refer to [Section 10.2](#) for details regarding recording of data.

Copies of pertinent records in connection with the study, including patient charts, laboratory data, etc., will be made available to Genzyme on request with due precaution towards protecting the privacy of the patient.

### **12.3.3 Record Retention**

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Essential documents are those documents, which individually and collectively, permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Any or all of the documents should be available for audit by the Sponsor's auditor and inspection by the regulatory authority(-ies).

### **12.3.4 Patient Discontinuation**

If a patient decides to discontinue participation in the study, he or she should be contacted in order to obtain information about the reason(s) for discontinuation and collection of any potential AEs. Whenever possible the patient should return to the clinic for the final clinical assessments. The Investigator will document the eCRF describing the reason for discontinuation.

### **12.3.5 Study or Site Termination**

If the Sponsor, Investigator, Clinical Monitor, or regulatory agencies discover conditions during the study that indicate that the study or site should be terminated, this action may be taken after appropriate consultation between the Sponsor, Investigator, and Clinical Monitor. Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study treatment
- Failure of the Investigator to comply with pertinent regulations
- Submission of knowingly false information from the research facility to the Sponsor, Clinical Monitor, or regulatory authorities
- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the guidelines for Good Clinical Practice, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

### **12.3.6 Monitoring**

A representative of Genzyme will visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with GCP regulations. It is the responsibility of the Investigator to be present or available for consultation during such scheduled monitoring visits. Direct access to all data pertaining to a patient's participation in this clinical investigation must be made available to the Clinical Monitor during these routine visits.

### **12.3.7 Materials Control**

#### **12.3.7.1 Receipt of Clinical Supplies**

Upon receipt of the clinical trial materials, the Investigator or designee must verify that the shipment was received as stated on the Clinical Supply Shipment Form (CSSF), enclosed within each shipment.

If the shipment was received as stated, the Investigator or designee must place a check mark (✓) in the Received/Verified box, and then sign and date the form. The form is then faxed to Genzyme (number listed on form) within 24 hours of receipt. If there are any discrepancies with the shipment Genzyme should be contacted immediately (contact information is listed on CSSF). A copy of this form must be retained in the site files.

#### **12.3.7.2 Disposition of Unused Clinical Supplies**

The Investigator will maintain accurate records of all clinical supplies that are received, dispensed, and either returned or destroyed. All used needles and syringes should be disposed of in accordance with institutional/clinic biohazard policies and precautions. The used, empty kits will be maintained in a limited access area until accounted for by a Genzyme Clinical Research representative.

If any unused material is remaining at the clinical site at study completion the material will be returned as instructed by Genzyme Europe B.V.

### **12.3.8 Warnings, Precautions, Contraindications**

For specific information concerning warnings, precautions, and contraindications, the Investigator is asked to refer to the appropriate section of the investigational labelling and Investigator Brochure.

### **12.3.9 Disclosure of Data**

All information obtained during the conduct of this study will be regarded as confidential and written permission from Genzyme is required prior to disclosing any information relative to this study. Manuscripts prepared for publication will be in accordance with the policy established and agreed to between the Investigator and Genzyme. Submission to the Sponsor for review and comment prior to submission to the publisher will be required. This requirement should not be construed as a means of restricting publication, but is intended solely to assure concurrence regarding data, evaluations, and conclusions and to provide an opportunity to share with the Investigator any new and/or unpublished information of which he/she may be unaware.

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## 14. APPENDICES

### 14.1 Common Pain and OA Medications

Common pain and OA medications are summarised below in Table 14-1 (Permitted Medications) and Table 14-2 (Medications that are Not Permitted).

**Table 14-1 Common Pain and OA Medications *Whose Use Is Permitted* (≤ 24-Hour Washout)**

Generic Name	Average Plasma Half-Life (hours)	Wash-Out (days)
Aceclofenac	3	1
Acetaminophen/paracetamol	2	1
Aspirin Enteric-coated Aspirin	Parent – 15 to 30 min Dose dependent Low (300 to 600 mg) = 3	1 Low – 1
Choline Magnesium Trisalicylate	Dose dependent Low = 2 to 3	Low - 1
Choline Salicylate	Dose dependent Low = 2 to 3	Low - 1
Dexketoprofen	0.35 to 1.6	12 hours
Diclofenac Sodium	2	1
Fenoprofen Calcium	2.5 to 3	1
Ibuprofen	2	1
Indomethacin	4.5	1
Ketoprofen	1 to 4	1
Sodium Meclofenamate	2 to 3.3	1
Mefenamic Acid	3.5	1
Tiaprofenic Acid	1.5 to 2.5	12 hours
Tolmetin Sodium	2	1

**Table 14-2 Common Pain and OA Medications *Whose Use Is Not Permitted*  
 (> 48-Hour Washout)**

<b>Generic Name</b>	<b>Average Plasma Half-Life (hours)</b>	<b>Wash-Out (days)</b>
Aspirin Enteric-coated Aspirin	Mid dose (after 1 g) = 5 to 6 High dose = 10 hours	Mid/High - 2
Celecoxib	11	2
Choline Magnesium Trisalicylate	Dose dependent High = 30	High - 6
Choline Salicylate	Dose dependent High = 30	High - 6
Difnisal	8 to 12	3
Etodolac	7	2
Etodolac ER	8	3
Fenbufen	10	3
Flurbiprofen	5 to 6	2
Ketoprofen SR	5.4	2
Ketorolac Tromethamine	2 to 8	2
Meloxicam	20	5
Nabumetone	24	5
Naproxen	12 to 15	3
Oxaprozin	40 to 50	9
Piroxicam	45 to 50	9
Rofecoxib	17	4
Salsalate	7 to 8 hours	2
Sulindac	8 Parent 17 Metabolite	4
Tenoxicam	70	17

## 14.2 The Kellgren-Lawrence Grading System of Osteoarthritis

The Kellgren-Lawrence Grading System of Osteoarthritis is summarised in Table 14-3.

**Table 14-3 The Kellgren-Lawrence Grading System of Osteoarthritis**

<b>Radiographic Criteria for Assessment of OA</b>		
Grade 0	None	No features of OA
Grade 1	Doubtful	Minute osteophyte, doubtful significance
Grade 2	Minimal	Definite osteophyte, unimpaired joint space
Grade 3	Moderate	Moderate diminution of joint space
Grade 4	Severe	Joint space greatly impaired with sclerosis of subchondral bone