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## TITLE PAGE

**DOCUMENT:** Statistical Analysis Plan  
**PROTOCOL:** SYNV00704  
A Multi-centre, Parallel, Double-Blind, Blinded Evaluator,  
Randomised, Placebo-controlled Evaluation of the Efficacy and Safety  
of a Single Dose of 6 mL of Synvisc in Patients with Symptomatic  
Osteoarthritis of the Knee

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# **STATISTICAL ANALYSIS PLAN**

**Protocol Number: SYNV00704**

**Final: 10 Oct. 2006**

**A Multi-centre, Parallel, Double-Blind, Blinded  
Evaluator, Randomised, Placebo-controlled Evaluation  
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the Knee**

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## **1.3 List of Appendices**

Data Listings are presented for all collected data for each patient.

### **16.2.1 Discontinued Patients**

<u>Appendix #</u>	<u>Appendix Title</u>
16.2.1-1	Listing of Patients Who Discontinued Prematurely from Study

### **16.2.2 Protocol Deviations**

<u>Appendix #</u>	<u>Appendix Title</u>
16.2.2-1	Listing of Screening Inclusion Criteria
16.2.2-2	Listing of Screening Inclusion Criteria Violations
16.2.2-3	Listing of Screening Exclusion Criteria
16.2.2-4	Listing of Screening Exclusion Criteria Violations
16.2.2-5	Listing of Baseline and Week 26 Eligibility Criteria
16.2.2-6	Listing of Baseline and Week 26 Eligibility Criteria Violations Only
16.2.2-7	Listing of Positive Pregnancy Test Results
16.2.2-8	Listing of Other Protocol Deviations

### **16.2.3 Patients Excluded from the Efficacy Analysis**

<u>Appendix #</u>	<u>Appendix Title</u>
16.2.3-1	Listing of Patients Enrolled, with Status Indicators for Randomization and Inclusion in Analysis Populations
16.2.3-2	Listing of Patients Excluded from Efficacy Analyses

### **16.2.4 Demographic Data**

<u>Appendix #</u>	<u>Appendix Title</u>
16.2.4-1	Listing of Patient Accountability
16.2.4-2	Listing of Demographic and Baseline Characteristics
16.2.4-3	Listing of Target Knee History
16.2.4-4	Listing of Contralateral Knee and Hip History
16.2.4-5	Listing of OA Treatment History
16.2.4-6	Listing of OA Treatment History of the Target Knee
16.2.4-7	Listing of OA Medication History of the Target Knee
16.2.4-8	Listing of Target Knee Assessment

- 16.2.4-9 Listing of Target Knee X-ray Assessment and Findings
- 16.2.4-10 Listing of Medical/Surgical History
- 16.2.4-11 Listing of Prior Medications
- 16.2.4-12 Listing of Prior Treatments
- 16.2.4-13 Listing of Concomitant Medications
- 16.2.4-14 Listing of Concomitant Treatments
- 16.2.4-15 Listing of Medication Assessment (Medication Washout and Restricted Medications)

### **16.2.5 – Drug Administration**

- 16.2.5-1 Listing of Administration of Investigational Study Treatment

### **16.2.6 Individual Efficacy Response Data**

<u>Appendix #</u>	<u>Appendix Title</u>
16.2.6-1	Listing of Efficacy Data Collected
16.2.6-2	Listing of WOMAC Subscale A Scores
16.2.6-3	Listing of OMERACT-OARSI
16.2.6-4	Listing of COGA Score
16.2.6-5	Listing of PTGA Score
16.2.6-6	Listing of WOMAC A1 Score
16.2.6-7	Listing of WOMAC Subscale B Scores
16.2.6-8	Listing of WOMAC Subscale C Scores
16.2.6-9	Listing of Total WOMAC Scores
16.2.6-10	Listing of Rescue Medication Usage

### **16.2.7 Adverse Event Listings**

<u>Appendix #</u>	<u>Appendix Title</u>
16.2.7-1a	Listing of Treatment-Emergent Adverse Event Data – Safety Population (includes 2 Parts: Target Knee and Other)
16.2.7-1b	Listing of Treatment-Emergent Adverse Event Data – Repeat Safety Population (includes 2 Parts: Target Knee and Other)
16.2.7-2a	Listing of Pre-Treatment Adverse Event Data – Enrolled Population (includes 2 Parts: Target Knee and Other)

### **16.2.8 Vital Signs and Physical Exams**

- 16.2.8-1 Listing of Vital Signs
- 16.2.8-2 Listing of Physical Examinations

## **2. DESCRIPTION OF THE PROTOCOL**

### **2.1 Number**

SYNV00704

## **2.2 Title**

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

## **2.3 Date**

The date of the original protocol is 15 November 2004.

## **2.4 Amendment**

The date of the first amendment is 12 January 2005.

The date of the second amendment is 19 September 2005.

## **2.5 Study Initiation and Completion**

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

## **2.6 Description of the Clinical Trial**

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

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).

During the treatment phase, 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.

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 re-assessed at Week 26 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 receive Synvisc treatment, regardless of their previous treatment allocation in the Blinded Phase.

The same rules and procedures regarding prohibited medications (as described above for the Treatment Phase) will continue to apply throughout the Repeat Treatment Phase.

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.

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.

## **2.7 Power and Sample Size**

Approximately 250 patients with symptomatic primary OA of the knee will be randomised. Sample size estimation is based on the mean treatment difference in the change from Baseline in the primary efficacy analysis of the primary efficacy variable: WOMAC LK 3.1 A.

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*).

### **3. OBJECTIVES**

The objectives of this study are 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.

#### **4. ANALYSIS POPULATIONS**

The following analysis populations will be used:

##### **4.1 All Patients Enrolled**

The All Patients Enrolled population will include all patients who sign an informed consent.

##### **4.2 Intent-to-Treat**

The Intent-to-Treat population will include all patients who are randomized to study treatment (Day 0).

##### **4.3 Per-Protocol**

The Per-Protocol population will include all patients who undergo any study treatment (Day 0) and have no major protocol violations affecting their efficacy assessments. Protocol violations will be reviewed by the study team prior to database lock to determine which violations disqualify the patient from the Per-Protocol analysis. The data will remain blinded when these assessments are made.

The following is a preliminary list of criteria that may disqualify a patient from the Per-Protocol analysis. This list is simply suggestive and is subject to change at the pre-lock review.

1. Intake of prohibited treatment/medication during the study that would affect their efficacy assessment.
2. Rescue medication taken within 48 hours of the study visit and the visit was not rescheduled.
3. Baseline WOMAC A score out of acceptable range.
4. Baseline WOMAC A1 score out of acceptable range.
5. The study treatment regimen was not completed.
6. Did not complete the study.
7. Visit performed outside of acceptable time window.
8. Kellgren-Lawrence grade IV / no osteophyte at Baseline in the tibio-femoral compartment
9. Kellgren-Lawrence grade IV in the patello-femoral compartment
10. Secondary OA
11. Tense effusion at Baseline

12. Received viscosupplementation in any joint within 9 months prior to Screening (i.e., violated exclusion criterion #5)
13. Had symptomatic OA of the contralateral knee or of either hip that was not responsive to paracetamol and required other therapy (i.e., violated exclusion criterion #14)
14. Had systemic or intra-articular injection of corticosteroids in any joint within 3 months prior to Screening (i.e., violated exclusion criterion #15).
15. Other violations deemed as disqualifying from Per-Protocol analysis

The above list is preliminary and may be modified during the data review meeting.

#### **4.4 Safety**

The Safety population will include all patients who undergo any study treatment.

#### **4.5 Repeat Safety**

The Repeat Safety population will include all patients who undergo any study treatment at Day 0 of the Repeat Treatment Phase.

### **5. DEFINITIONS**

#### **5.1 Age**

Age will be presented as the number of years between date of birth and date of signed informed consent. Age is computed in whole years as follows:

$$\text{Age} = (\text{YEAR}(\text{consent}) - \text{YEAR}(\text{DOB})) - (\text{MONTH}(\text{consent}) < \text{MONTH}(\text{DOB})) \\ - (\text{MONTH}(\text{consent}) = \text{MONTH}(\text{DOB})) * (\text{DAY}(\text{consent}) < \text{DAY}(\text{DOB}))$$

where “YEAR,” “MONTH,” and “day,” are SAS functions and the comparisons

$(\text{MONTH}(\text{consent}) < \text{MONTH}(\text{DOB}))$  and

$(\text{MONTH}(\text{consent}) = \text{MONTH}(\text{DOB}))$

return values of 1 or 0 when the comparison is true or false, respectively.

#### **5.2 Analysis Sites**

Study site will be included in the efficacy analyses as a factor variable. Sites with less than 4 patients randomized will be pooled into a single category.

#### **5.3 Early Termination Visit**

Whenever possible, patients who discontinue prematurely after receiving at least 1 injection of Synvisc or PBS should return to the clinic for the final (Week 26) evaluations. These visits by patients who are discontinuing the trial will be referred to as early termination (ET) visits. For patients who discontinued the study and returned for an ET visit, the ET target knee assessment,

rescue medication, WOMAC, COGA, PTGA data will be presented not as Week 26, but as closely as possible to the appropriate scheduled study week. With respect to vital sign, physical examination, and pregnancy test data, which were only collected at Week 26/ET during the post-baseline visits, the ET data will be presented as Week 26 data. For those patients who did not return to complete an ET visit, the last visit collected will be summarized at the study week associated with that visit along with data from patients who continued past that study week. These patients will not contribute to the ET vital sign, physical examination, and pregnancy test data, because these data will not have been collected at the patient's last visit.

#### **5.4 Baseline**

Baseline is defined as the value observed prior to dosing. Missing Day 0 values will be replaced by Screening values.

#### **5.5 Change from Baseline**

Change from Baseline is defined as the absolute difference between the Baseline value obtained at Study Day 0 and the respective time point. Negative values represent decreases from Baseline; positive values will reflect increases from Baseline.

#### **5.6 Percent Change from Baseline**

Percent change from Baseline is defined as the change from Baseline divided by the Baseline value times 100%:

$$100\% \times (\text{Post-Baseline value minus Baseline value})/(\text{Baseline value})$$

#### **5.7 Improvement from Baseline**

Improvement from Baseline is defined as the absolute difference between the Baseline value obtained at Study Day 0 and the respective time point. Negative values represent a negative improvement from Baseline; positive values will reflect a positive improvement from Baseline.

#### **5.8 Length of Time**

Except for age, the length of time between 2 reference dates will be calculated as the number of calendar days between the two dates plus one day. When the length of time between 2 reference dates is expressed in months, the number of months will be calculated as the number of calendar days between the 2 dates plus 1 day divided by 30.4 days. When the length of time between 2 reference dates is expressed in weeks, the number of weeks will be calculated as the number of calendar days between the 2 dates plus 1 day divided by 7 days. Months and weeks will be rounded to 1 decimal place prior to summary.

#### **5.9 Imputation of Dates**

Some dates are used in computations of intervals between times, such as times between diagnosis of OA and Screening. In this case, the "end date" is the date of Screening (or

Baseline), but the start date may be missing or partially missing. When the start date is missing or partially missing and is prior to Screening (and “end date is known, such as the date of screening), computations will be handled as follows:

- (a) if all parts of a date are missing, the value for the date remains missing
- (b) if only the day is missing (and month is present), then:
  - (i) if the month of screening > the month of the partially known date, then impute the 15th of the month for the missing day
  - (ii) if the month of screening = the month of the partially known date, then impute the day that is the midpoint between first of month and date of screening.
- (c) if the day and month are missing, then:
  - (i) if the year of screening is > the year of the partially known date, then impute July 1 of the year of date
  - (ii) if the year of screening = year of the partially known date = X, impute the day and month that are the midpoint between Jan 1, 200X and screening date in 200X.

Round to the earlier date if either of 2 days could be the midpoint. After applying this algorithm, the imputed date is to be used in the computation of the time interval.

When the first date is missing or partially missing and is known to follow Screening (e.g., dosing dates necessary for the computation of total dosage of rescue medications), computations will be handled as follows:

Start dates will be imputed using the earliest possible date, given external known information.

- (a) if all parts of a date are missing, the value for the date is imputed the first date of injection
- (b) if only the day is missing but month and year are known, then
  - (i) if the known month > month of injection, then impute first of the month of the missing date
  - (i) if the known month = the month of injection, then impute the day of injection
- (c) if the month is missing but year is known, then
  - (ii) if the known year > year of injection, then impute 01 January of the year of the missing date
  - (i) if the known year = the year of injection, then impute the date of injection

End dates will be imputed using the latest possible date, given known external information.

- (a) if all parts of a date are missing, the value for the date is imputed date of study completion/termination for the patient

- (b) if only the day is missing but the month and year are known, then
  - (i) if the known month < month of completion/termination, then impute last day of the month (see code below)
  - (ii) if the known month = the month of completion/termination, then impute the day of completion/termination
- (c) if the month is missing but year is known, then
  - (i) if the known year < year of completion/termination, then impute 31December of the year of the missing date
  - (ii) if the known year = the year of completion/termination, then impute the date of completion/termination

The date of the last day of the month can be computed as follows for a known MONTH and YEAR as follows:

```
start = input( '01/' || MONTH || '/' || YEAR, date11. );  
lastday = intnx ('month', start, 0, 'end');
```

## 5.10 Prior and Concomitant Medication/Treatment

Prior medications or treatments are defined as any medication or therapy taken by the patient within 1 month prior to Baseline. A medication or treatment is considered concomitant if it is taken at any time on or after the Baseline visit up to and including the day of the final study evaluation (the Week 26 visit or the early termination visit). A medication taken prior to Baseline and continuing past Baseline is considered both prior and concomitant.

For the Repeat Treatment Phase, a medication or treatment is considered concomitant if it is taken at any time after the Repeat Day 0 visit up to and including the Repeat Week 4 visit. Prior medications or treatments will not be defined for the Repeat Treatment Phase, as these are the medications considered concomitant in the Treatment Phase.

## 5.11 WOMAC Subscale Score

The WOMAC is composed of 3 subscales (A: Pain, B: Stiffness, C: Physical Function). Each subscale contains components that are scored using a Likert Scale. 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. There are 5 components for subscale A (Pain), 2 components for subscale B (Stiffness), and 17 components for subscale C (Physical Function). A WOMAC subscale score is calculated as the mean of the available component scores within the subscale:

$$\text{WOMAC subscale score} = \frac{\text{sum}(\text{response for non-missing subscale components})}{(\text{number of non-missing subscale components})}$$

The subscale score will be set to missing according to the following: if  $\geq 2$  Pain components are missing, if both Stiffness components are missing, if  $\geq 4$  Physical Function components are missing (Bellamy, 2003, *J Rheumatol*). If there are missing components within a subscale but the number of missing components does not meet the criteria for setting the subscale score to missing, then the value of the missing components will be set equal to the mean of the available components of the respective subscale.

#### **5.12 WOMAC Total Score**

The total WOMAC score is computed as the sum of the 3 WOMAC subscale responses. The total WOMAC score ranges from 0 to 96 since the subscale responses range from 0 to 20 for the WOMAC A subscale, 0 to 8 for the WOMAC B subscale, and 0 to 68 for the WOMAC C subscale. The total WOMAC score will be set to missing if any of the WOMAC subscale scores are set to missing as defined in Section 5.9, above; if there are some missing values in a WOMAC subscale score but each WOMAC subscale score used was computed, then the computation of the total WOMAC score will use the imputed mean values for the subscales, as defined above. (Computationally the total WOMAC score =  $5 \times$  WOMAC A mean score +  $2 \times$  WOMAC B mean score +  $17 \times$  WOMAC C mean score.)

#### **5.13 Last Observation Carried Forward**

For the analysis of the percentages of positive responders, patients who discontinue the study prior to the Week 26 assessment due to either target knee-related AEs or due to lack of efficacy will be classified as non-responders in the efficacy analysis. Patients who discontinue the study for other reasons will have the responder status imputed using the last observation carried forward (LOCF) method. The LOCF will be used for all responder analyses, but it will not be used for the analysis of other parameters.

#### **5.14 OMERACT-OARSI Responder**

Patients will be classified as responders (yes/no) at each post-baseline visit using a modified version of the OMERACT-OARSI set of responder criteria (Pham et al., 2003, *J Rheumatol*; Pham et al., 2004, *Osteoarthritis Cartilage*). For the OMERACT-OARSI set of responder criteria, a function of the WOMAC A (pain) and C (physical function) subscores and the PTGA will be used. A patient will be classified as a positive responder if at least one of the following two conditions is observed at the post-baseline assessment:

- In either pain (WOMAC A subscore) or function (WOMAC C subscore), a high improvement in the subscore, where high improvement in a subscore is achieved if there is both a  $\geq 50\%$  improvement from Baseline and an absolute change from Baseline of  $\geq 20$  NU (normalized units)
- Improvement in at least 2 of the following 3:

1. Improvement in pain (WOMAC A subscore) defined as  $\geq 20\%$  improvement from Baseline and an absolute change from Baseline of  $\geq 10$  NU
2. Improvement in function (WOMAC C subscore) defined as  $\geq 20\%$  improvement from Baseline and an absolute change from Baseline of  $\geq 10$  NU
3. Improvement in PTGA defined as  $\geq 20\%$  improvement from Baseline and an absolute change from Baseline of  $\geq 10$  NU (Note: A change of 1 unit will result in a change of  $> 20\%$  because Baseline values are 0,1, 2, 3, and 4 so the smallest percent change is  $100\% \times 1/4 = 25\%$ .)

Values expressed as normalized units (NU) are recoded scores presented on a 0-100 range, by dividing the score by the maximum possible value of the score, all multiplied by 100.

## 6. PATIENT ACCOUNTABILITY

All patients enrolled in the study (signed informed consent) will be included in the summary of patient accountability. Frequencies and percentages of patients enrolled will be summarized for each site by treatment group and for both groups pooled overall (i.e., the “total” group); a similar table will be displayed for the randomized patients. Frequencies and percentages of the following patient groups will be summarized by treatment group and overall: total number of patients enrolled, number of screen failures, number of rescreened patients, number of patients randomized (ITT population), number of patients receiving at least one study injection (Safety population), number of patients in the Per-Protocol population. Additionally, for the ITT population, the number of patients completing study, number of patients not completing study, number of patients not completing study summarized by specific reason (adverse experience, non-compliant, wishes to withdraw, lost to follow-up, other), the number of patients eligible for the Repeat Treatment Phase, the number of patients receiving at least one study injection in the Repeat Treatment Phase (Repeat Safety population), the number of patients completing the final (Week 4) Repeat Treatment Phase visit, and reasons for discontinuing from the Repeat Treatment Phase.

In addition, a summary of the number of patients presenting at each visit will be provided for all patients enrolled. A similar summary of the number of patients presenting at each repeat treatment visit will be provided for all patients in the Repeat Safety population.

The following will also be provided to summarize patient accountability: a listing of patients who discontinued prematurely from the study, a summary of the reasons patients were ineligible for the Per-Protocol analyses, and a listing of enrolled patients that includes indications of the randomization (treatment given, or indication of that the patient was not randomized) and flags each patient’s inclusion in each analysis population. In addition a listing of patients that were excluded from the efficacy analyses (per-protocol population) and the reasons for exclusion are provided. A listing of inclusion/exclusion criteria will be presented in addition to a listing of protocol deviations.

## **7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS**

The summaries of demographic and baseline characteristics will be presented for the ITT population by treatment group and overall. For categorical data, frequencies and percentages will be provided and, for continuous data, descriptive statistics, including sample size, mean, median, standard deviation, and range of values (i.e., minimum and maximum values) will be provided. No inferential statistics will be presented. All information to be summarized will also be presented in listings.

### **7.1 Demographics**

Summary statistics will be from the data collected at Screening for the measurements listed below:

- Age
- Sex
- Race
- Weight
- Height
- Body mass index

This summary will also be presented for the Repeat Safety population by prior treatment group and overall.

### **7.2 Target Knee History**

Target knee history will be summarized for the following variables:

- Knee to be treated (Right/Left)
- Origin of Target Knee OA (Idiopathic-Primary, Secondary)
- Time since initial diagnosis of OA in the Target Knee (months)
- Chondrocalcinosis (Yes/No)
- Significant valgus/varus deformities (Yes/No)
- Significant ligamentous laxity (Yes/No)
- Significant meniscal instability (Yes/No)

This summary will also be presented for the Repeat Safety population by prior treatment group and overall.

### **7.3 OA of the Contralateral Knee and of Either Hip**

Additional joint OA histories will be summarized as follows for patients in the Safety population:

- Symptomatic OA in the contralateral knee (Yes/No)
  - If yes, Responsive to Paracetamol (Yes/No)
  - If yes, Requires Other Therapy (Yes/No)
- Symptomatic OA in the either hip (Yes/No)
  - If yes, Responsive to Paracetamol (Yes/No)
  - If yes, Requires Other Therapy (Yes/No)

This summary will also be presented for the Repeat Safety population by prior treatment group and overall.

### **7.4 OA Treatment History**

OA treatment history will be summarized for the following variables for patients in the Safety population:

- Prior viscosupplementation in the Target Knee
  - Yes/No
  - Time since last viscosupplementation (months)
- Prior viscosupplementation in any other joint
  - Yes/No
  - Time since last viscosupplementation (months)
- Prior intra-articular injection of corticosteroids in the Target Knee
  - Yes/No
  - Time since last intra-articular injection of corticosteroids (months)
- Prior intra-articular injection of corticosteroids in any other joint
  - Yes/No
  - Time since last intra-articular injection of corticosteroids (months)
- Prior arthrocentesis in the Target Knee
  - Yes/No
  - Time since last arthrocentesis (months)

- Prior arthroplasty in the Target Knee
  - Yes/No
  - Time since last arthroplasty (months)
- Prior arthroscopy in the Target Knee
  - Yes/No
  - Time since last arthroscopy (months)
- Prior other surgical procedures in the Target Knee
  - Yes/No
  - Time since last other surgical procedures
- Undergoing physical therapy for the lower extremities
  - Currently Yes/No
  - Within one month before Screening Yes/No
- Currently using a brace or other assistive device
  - Yes/No

### **7.5 OA Medication History of the Target Knee**

Osteoarthritis-specific medications will be documented at Screening by determining if a patient is taking or has ever taken any of the following:

- NSAIDS
- Analgesics
- Narcotics
- Glucosamine
- Chondroitin sulphate
- Diacerhein
- Avocado/soya extracts
- Other

The frequencies and percentages of patients in the Safety population taking medications in these categories will be summarized.

## 7.6 Target Knee Assessment

The Target Knee assessment for patients in the Safety population will be summarized at Screening by the following:

- Experienced in the past year
  - Pain (Yes/No)
  - Tenderness (Yes/No)
  - Swelling (Yes/No)
  - Stiffness (Yes/No)
  - Warmth (Yes/No)
  - Redness (Yes/No)
  - Other (Yes/No)

The Target Knee Assessment will be summarized at Screening, Day 0, Weeks 1, 4, 8, 12, 18, and 26 and again for the Repeat Safety population adding Repeat Weeks 1 and 4 to the display. The tables will be presented by the following:

- Present today
  - Pain (None/Mild/Moderate/Severe)
  - Tenderness (None/Mild/Moderate/Severe)
  - Swelling (None/Mild/Moderate/Severe)
  - Effusion (None/Mild/Moderate/Severe)
  - Stiffness (None/Mild/Moderate/Severe)
  - Warmth (None/Mild/Moderate/Severe)
  - Redness (None/Mild/Moderate/Severe)
  - Other (None/Mild/Moderate/Severe)

## 7.7 X-Ray Assessment and Findings of the Target Knee

The X-ray assessment will be summarized by the following:

- Available X-ray views
  - Antero-posterior, weight bearing
    - Yes/No
    - Time since last antero-posterior x-ray (months)

- Profile view
  - Yes/No
  - Time since last profile view x-ray (months)
- Femoro-patellar
  - Yes/No
  - Time since last femoro-patellar view x-ray (months)
- Tibio-femoral Joint Assessment
  - Compartment with most severe features of OA
    - Medial/Lateral
    - Kellgren-Lawrence Grade (0/I/II/III/IV)
  - Patello-femoral Joint Assessment
    - Kellgren-Lawrence Grade (0/I/II/III/IV)

## **7.8 Medical/Surgical History**

Summaries of medical/surgical histories by body system will be presented. The presence, absence or missing status of each body system and, if present, whether the condition is current or non-current will be summarized as frequencies and percentages; all frequencies will be based on the total number of patients in the Safety population. The body systems will be ordered by decreasing frequency based on the overall group. Patients will be counted once with respect to the presence, absence, or missing status of a condition in each body system; if present, the patient will be counted once for conditions that are current and once for conditions that are not current. These data are only collected at Screening and will not be presented for the Repeat Treatment Phase.

## **7.9 Prior Medications**

Summaries of prior medications by drug class and medication (coded) will be presented, with drug class and medications under each class ordered by decreasing frequency based on the overall group. Patients will be counted once for each unique medication and may have received more than one unique medication. In the summary over medications for each drug class, each patient will be counted once for each unique drug class. A separate summary will be provided by medication, sorted by frequency based on the overall group. Patients will be counted once for each unique medication and may have received more than one unique medication. These tables will be presented for the Initial Phase based on the Safety population.

### **7.10 Prior Treatments**

Summaries of prior treatments by system organ class and preferred term will be presented, with system organ class and preferred terms under each class ordered by decreasing frequency based on the overall group. Patients will be counted once for each unique treatment and may have received more than one unique treatment. In the summary over treatments for each system organ class, each patient will be counted once for each unique system organ class. A separate summary will be provided by treatments, sorted by frequency based on the overall group. Patients will be counted once for each unique treatment and may have received more than one unique treatment. These tables will be presented for the Treatment Phase based on the Safety population.

### **7.11 Washout Period**

Data from the washout period will be summarized for the Safety population by treatment group and overall as follows:

- Medication Washout Period Required at Screening (Yes/No)
- Did the patient washout from all prohibited medications prior to Day 0 (Baseline) (Yes/No)
- Were prohibited medications discontinued at least 48 hours prior each visit (by visit) (Yes/No)

The discontinuation of prohibited medications at each visit will also be summarized for the visits during the Repeat Treatment Phase for the Repeat Safety population.

### **7.12 Administration of Investigational Study Treatment**

The following information regarding the administration of investigational study treatment will be summarized by treatment group for each injection (the injection for the Treatment Phase and, for applicable patients, the injection for Repeat Treatment Phase):

- Use of topical anesthetic (Yes/No)
- Use of local anesthetic (Yes/No)
- Approach for study injection (Lateral infra-patellar/Supra-patellar/Medial infra-patellar/Other)
- Synovial fluid/effusion removed during arthrocentesis
  - Yes/No
  - If Yes, volume aspirated (mL)
- Full volume of study treatment injected (Yes/No)

- Needle gauge (18/20/Other)

## **8. EFFICACY**

In all efficacy analyses, the following convention will be used: treatment differences will be computed to show the difference (Synvisc result minus placebo result); odds ratios will be computed so that a ratio less than 1 favors Synvisc.

### **8.1 Primary Efficacy Endpoint**

The primary efficacy endpoint will be the WOMAC Subscale A mean change from Baseline over 26 weeks. This endpoint will be based on the WOMAC questionnaire which is a self-administered, health status measure used to probe symptoms of pain, stiffness, and physical function in patients with OA of the hip and/or knee. The index consists of a total of 24 questions that are divided into three subscales: A. pain (5 questions), B. stiffness (2 questions) and C. physical function (17 questions).

#### **8.1.1 WOMAC Subscale A Mean Change from Baseline over 26 weeks**

The WOMAC Subscale A score for each patient visit will be computed as described in Section 5.9. The mean change for each treatment group and the contrast of the mean changes will be estimated using repeated measures ANCOVA, as described in Section 12.2.

Estimates of treatment effects will also be presented for the observed data.

### **8.2 Secondary Efficacy Endpoints**

Unless otherwise specified, the secondary efficacy endpoints will be used to compare the treatment effects of Synvisc and Placebo on absolute change from Baseline over 26 weeks and absolute change from Baseline at each post-baseline efficacy visit (Weeks 4, 8, 12, 18 and 26). For continuous outcomes, these treatment differences will be estimated using the repeated measures ANCOVA described in Section 12.2. Unless otherwise specified, for binary outcomes these treatment differences will be estimated using generalized estimating equations (GEE) for repeated binary outcomes; and for multinomial outcomes, these treatment differences will be estimated using proportional odds logistic regression with generalized estimating equations.

#### **8.2.1 OMERACT-OARSI Responder**

Patients will be classified as responders (yes/no) at each post-baseline visit using the OMERACT-OARSI set of responder criteria as described in Sections 5.13 and 5.14 above.

The OMERACT-OARSI set of responder criteria is a composite index based on 3 symptomatic domains and was developed to define a priori which patients experience clinically significant responses to therapy in OA clinical trials.

Using the OMERACT-OARSI responder criteria, patients will be classified as responders (yes/no) at each post-baseline visit. Patients who withdraw prior to the post-baseline visit due to either target knee-related AEs or due to lack of efficacy will be classified as non-responders. Patients who discontinue the study for other reasons will have the responder status imputed, carrying forward the most recent status.

These data will be analyzed using GEE for repeated binary outcomes.

The OMERACT-OARSI responder criteria require both an absolute change and a relative change and consider both pain and function as important domains. It is a validated and accepted measure of clinically meaningful improvement in clinical trials of hip and knee OA symptoms (Schnitzer, 2003, *Arthritis Rheum*; Bayat et al., 2005, *APLAR Journal of Rheumatology*). Since its publication in 2004 (Pham et al., 2004, *Osteoarthritis Cartilage*), this responder analysis has been used as an efficacy endpoint in several randomized, controlled trials in OA to assess a clinically meaningful response to a therapeutic intervention (Sheldon et al., 2005, *Clin Ther*; Fleischmann et al., 2006, *Clin Rheumatol*; Lehmann et al., 2005, *Curr Med Res Opin*; Clegg et al., 2006, *NEJM*). The OMERACT-OARSI responder criterion is therefore considered the most important secondary efficacy endpoint in this study.

### **8.2.2 WOMAC Subscale A 26-Week Change from Baseline**

The WOMAC Subscale A pain score for each patient visit will be computed as described in Section 5.11. The range of possible values for this subscale is 0 to 4, with high values indicating more severe pain. The change from Baseline to Week 26 for each treatment group and the contrast of the change will be estimated as will the change from Baseline to each post-baseline assessment.

Treatment groups will be compared, and estimates of the treatment effects will be presented based on the repeated measures ANCOVA described in Section 12.2. Estimates of treatment effects will also be presented based on a similar repeated measures model of the observed data.

### **8.2.3 WOMAC A1**

The WOMAC A1 is an assessment of walking pain on a flat surface within the past 48 hours and will be quantified using a Likert Scale (0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Extreme).

At each post-baseline visit, patients will be classified into responder category (yes/no). Those patients with at least a 1-category improvement from baseline will be considered responders; all others will be considered non-responders. For responder analyses, LOCF will be applied as described in Sections 5.13. These data will be analyzed over all post-baseline visits and at each post-baseline visit using GEE for binary outcomes.

The post-baseline Likert Scale data will be analyzed over all post-baseline visits and at each post-baseline visit using proportional odds logistic regression. LOCF will not be applied to the

data for this analysis. The data will be presented as a frequency of responses at each visit, by treatment group. In addition, displays that treat the Likert data as continuous data will be presented as a post-hoc addendum outside of this SAP.

#### **8.2.4 WOMAC Subscale C**

The WOMAC Subscale C assesses the patient-relevant symptoms in physical functions and consists of seventeen questions. The range of possible values for this subscale is 0 to 4, with high values indicating more severe limitations to physical functions.

In the secondary efficacy analysis, absolute change from Baseline for Weeks 4, 8, 12, 18 and 26 will be explored including the overall change as well as the change at each post-baseline visit.

Treatment groups will be compared, and estimates of the treatment effects will be presented based on the repeated measures ANCOVA described in Section 12.2. Estimates of treatment effects will also be presented based on a similar repeated measures model of the observed data.

#### **8.2.5 PTGA of the Target Knee OA**

The patient will give a global self-assessment of target knee OA condition using a Likert Scale (0=Very Well, 1=Well, 2=Fair, 3=Poor, 4=Very Poor).

At each post-baseline visit, patients will be classified into responder category (yes/no). Those patients with at least a 1-category improvement from baseline will be considered responders; all others will be considered non-responders. For responder analyses, LOCF will be applied as described in Section 5.13. These data will be analyzed over all post-baseline visits and at each post-baseline visit using GEE for binary outcomes.

The post-baseline Likert Scale data will be analyzed over all post-baseline visits and at each post-baseline visit using proportional odds logistic regression. LOCF will not be applied to the data for this analysis. In addition, displays that treat the Likert data as continuous data will be presented as a post-hoc addendum outside of this SAP.

#### **8.2.6 COGA of the Target Knee OA**

The masked clinical observer will give a global assessment of the target knee OA using a Likert Scale (0=Very Well, 1=Well, 2=Fair, 3=Poor, 4=Very Poor).

At each post-baseline visit, patients will be classified into responder category (yes/no). Those patients with at least a 1-category improvement from baseline will be considered responders; all others will be considered non-responders. For responder analyses, LOCF will be applied as described in Section 5.13. These data will be analyzed over all post-baseline visits and at each post-baseline visit using GEE for binary outcomes.

The post-baseline Likert Scale data will be analyzed over all post-baseline visits and at each post-baseline visit using proportional odds logistic regression. LOCF will not be applied to the

data for this analysis. In addition, displays that treat the Likert data as continuous data will be presented as a post-hoc addendum outside of this SAP.

### **8.3 Tertiary Efficacy Endpoints**

Unless otherwise specified, the tertiary efficacy endpoints will be used to compare absolute change from Baseline over 26 weeks and for each post-baseline efficacy visit (Weeks 4, 8, 12, 18 and 26) between the Synvisc and PBS treatment groups.

#### **8.3.1 Total WOMAC Score**

The total WOMAC score is computed as described in Section 5.12. If one subscale is missing, then the total WOMAC score is missing. The change in the Total WOMAC score will be analyzed over all post-baseline doses and at each post-baseline dose using the repeated measures ANCOVA described in Section 12.2. Estimates of treatment effects with respect to the change from baseline will be based on this model.

Estimates of treatment effects will also be presented based on a similar repeated measures model of the observed data.

#### **8.3.2 WOMAC Subscale B**

The WOMAC Subscale B assesses the patient-relevant symptoms in stiffness and consists of two questions. The range of possible values for this subscale is 0 to 4, with high values indicating more severe stiffness. The change in the WOMAC B score will be analyzed over all post-baseline doses and at each post-baseline dose using the repeated measures ANCOVA described in Section 12.2. Estimates of treatment effects with respect to the change from baseline will be based on this model.

Estimates of treatment effects will also be presented based on a similar repeated measures model of the observed data.

#### **8.3.3 Rescue Medication**

The mean daily consumption of paracetamol over 26 weeks will be presented and analyzed, as will the mean daily consumption of paracetamol between each successive post-baseline visit. The mean daily consumption will be compared at each post-baseline visit between treatment groups using the Wilcoxon Rank Sum test.

In the event that the start and stop dates are not sufficiently complete, the number of patients taking rescue medications over the course of the study will be presented. These data will be tested across treatment groups using the Cochran-Mantel-Haenszel test.

Summaries of the use of rescue medication during the Repeat Treatment Phase will be similar, but will not include any statistical inference.

## **8.4 Exploratory Efficacy Endpoints**

### **8.4.1 WOMAC Subscale A Responders at Week 26**

In addition to the OMERACT-OARSI, patients will be classified as “WOMAC Subscale A 20% Responders” if they complete the study and the Week 26 evaluation and have an improvement in the WOMAC Subscale A of at least 20% from Baseline. The proportion of responders in the treatment groups will be compared using logistic regression.

The patients will also be classified as “WOMAC Subscale A 50% Responders” and “WOMAC Subscale A 70% Responders” if they complete the study and the Week 26 evaluation and have an improvement in the WOMAC Subscale A of at least 50% from Baseline and at least 70% from Baseline, respectively. In each case, the proportion of responders in the treatment groups will be compared using logistic regression.

### **8.4.2 Percent Change from Baseline in WOMAC Scores**

For the WOMAC Subscale A, B, and C scores and the Total WOMAC score, the percent change from baseline will be analyzed and presented using the same analysis approach applied to the absolute change from baseline. Treatment differences at each post-baseline week and overall will be presented using the same modeling structure. Because normality of the data is an assumption underlying the model, the analyses of the percent change data may be a less desirable approach compared to the analysis of the changes on the original scale.

### **8.4.3 Dropouts Due to Lack of Efficacy**

The treatment differences in dropouts due to lack of efficacy will be examined using Kaplan-Meier estimates from PROC LIFETEST in SAS. In the analysis, patients will be censored when they complete the study or when they drop out due to some other reason. A Kaplan-Meier plot will be displayed to show any treatment differences, with the p-value from the log rank test added to the figure.

## **9. SAFETY**

### **9.1 Adverse Events**

Adverse events and serious adverse events are defined in Section 9.3.6 and 9.3.6.1 of the protocol. Additionally, local adverse events are defined as adverse events that are at least possibly related to study treatment and occur in the target knee within 48 hours of injection. Operationally, AEs “within 48 hours” of injection are defined as those AEs that that occurred on the day of injection or on either of the following 2 days.

Any observed or reported adverse event (AE) that occurs during the study (ending with and including the Week 26 or early termination visit) that are clinically significantly worse than those observed at Baseline will be recorded on the AE page of the electronic case report form

(eCRF). The clinical significance of target knee findings is defined in protocol Section 9.3.4; for other AEs clinical significance is defined in Section 9.3.6.

AEs manifesting at the time of or after the first study treatment will be categorized as treatment-emergent. AEs occurring prior to the first treatment will be labeled as pre-treatment emergent. The AEs are classified according to System Organ Class and Preferred Term via the MedDRA coding dictionary. The duration, severity, relationship to study treatment, action taken, and outcome of the AE are recorded, as are whether the event occurred at the target knee and whether the event was classified as a serious adverse event (SAE). The AEs are classified as related to the study treatment (i.e., study material) and/or related to the injection procedure.

With respect to the Repeat Treatment Phase, AEs manifesting at the time of or after the treatment will be categorized as treatment-emergent.

## **9.2 Vital Signs**

Vital signs will be measured at Screening, Baseline, and Week 26 and, for patients who continue into the Repeat Treatment Phase, at Repeat Day 0 and Repeat Week 4. Among patients in the Repeat Safety population, the Week 26 vital signs and the Repeat Day 0 vital signs are the same measurements. Vitals signs to be collected include:

- temperature
- heart rate
- respiratory rate
- blood pressure

## **9.3 Physical Examinations**

Physical examinations will be performed at Screening and Week 26 and, for patients who continue into the Repeat Treatment Phase, at Repeat Day 0 and Repeat Week 4. Among patients in the Repeat Safety population, the Week 26 vital signs and the Repeat Day 0 vital signs are the same measurements. Body systems examined will include:

- General appearance (mandatory)
- Skin (mandatory)
- Extremities/Joints (mandatory)
- Mental Status (mandatory)
- HEENT
- Lymph Nodes
- Heart

- Lungs
- Breasts
- Abdomen
- External Genitalia
- Pelvic
- Rectal
- Neurological

If a body system was not examined, “Not Examined” was to be recorded.

#### **9.4 Concomitant Medications**

Summaries of concomitant medications by drug class and medication (coded using the WHO Drug Dictionary) will be presented, with drug class and medications under each class ordered by decreasing frequency based on the overall group. Patients will be counted once for each unique medication and may have received more than one unique medication; in the summary (over medications) for each drug class, each patient will be counted once for each unique drug class. A separate summary will be provided by medication, sorted by frequency based on the overall group. Patients will be counted once for each unique medication and may have received more than one unique medication. These tables will be presented for the Treatment Phase based on the Safety population, and repeated for drugs taken during Repeat Treatment Phase, based on those patients in the Repeat Safety population. In the Repeat Treatment Phase summary, references to treatment groups will refer to the treatment received in the prior phase of the study.

Separate tables will summarize the use (yes/no) of chondroitin sulfate, glucosamine, avocado/soya extracts, or any of the above. One table will summarize use during the main study based on the Safety population, and a second table will summarize use during the Repeat Treatment Phase using the Repeat Safety population.

#### **9.5 Concomitant Treatments**

Summaries of concomitant treatments by drug class and preferred term will be presented, with drug class and preferred terms under each class ordered by decreasing frequency of treatments based on the overall group. Patients will be counted once for each unique treatment and may have received more than one unique treatment; in the summary (over treatments) for each system organ class, each patient will be counted once for each unique system organ class. A separate summary will be provided by treatments, with treatments sorted by frequency based on the overall group. Patients will be counted once for each unique treatment and may have received more than one unique treatment. These tables will be presented for the Treatment Phase based on the Safety population, and repeated for therapies received during Repeat Treatment Phase,

based on those patients in the Repeat Safety population. In the Repeat Treatment Phase summary, references to treatment groups will refer to the treatment received in the prior phase of the study.

## **10. ADDITIONAL ENDPOINTS**

There are no additional endpoints that need to be defined for the Study Report.

## **11. STUDY CONDUCT AND STATISTICAL IMPACT**

### **11.1 Protocol Amendments**

Protocol Amendment 1 was finalized on January 12, 2005. This amendment clarified some inclusion/exclusion criteria and the patient blinding procedure; changed the scale of the Patient Global Assessment from VAS to Likert; and added the WOMAC questionnaire, Patient Global Assessment, and Clinical Observer Global Assessment to the Appendices.

Protocol Amendment 2 was finalized on September 19, 2005. The changes made during this amendment included: a clarification to the list of prohibited treatments and medications; additions to the statistical methods that adverse events would be summarized by severity and relationship to study procedure and that target knee AEs would be summarized; and clarifications to the definition of clinically significant deterioration in target knee assessment to ensure that site staff would record only those events considered medically relevant.

### **11.2 Interim Safety Analysis**

An option to perform an interim analysis when 50% of patients completed their Week 8 visit was specified in the protocol. However, no interim analysis was performed.

## 12. STATISTICAL ANALYSIS

### 12.1 General Analysis Issues

#### 12.1.1 Missing or Invalid Data

The WOMAC subscale score will be set to missing according to the following: if  $\geq 2$  Pain components are missing, if both Stiffness components are missing, if  $\geq 4$  Physical Function components are missing (Bellamy, 2003, *J Rheumatol*). Otherwise the average of the remaining items will be used to impute the missing values.

For primary analyses, missing efficacy data will not be imputed. However, for the analysis of the percentages of positive responders, patients who discontinue the study prior to the Week 26 assessment due to either target knee-related AEs or due to lack of efficacy will be classified as non-responders in the efficacy analysis. Patients who discontinue the study for other reasons will have the responder status imputed using the LOCF method. (To clarify: If a patient is a responder or a nonresponder at a given visit, but at the next visit the patient does not have the all the data necessary to determine responder/non-responder status, then at the second visit: the individual data values from a previous visit *will not* be carried forward but the responder/non-responder determination of the previous visit *will* be carried forward.)

#### 12.1.2 Significance Level

The primary efficacy hypothesis test will be performed using a 5% overall significance level. For the secondary and tertiary efficacy endpoints, hypothesis tests will be performed individually at the 5% significance level and there will be neither adjustment for multiple tests nor adjustment for multiplicity of endpoints. All hypothesis tests will be performed with two-sided alternative hypotheses. The interaction effects will be tested at a 15% significance level.

#### 12.1.3 Reporting of Numeric Values

Summary statistics and estimates will be presented with one decimal place. Estimates of variation will be presented with two decimal places. All p-values will be rounded to 3 decimal places and presented as “<0.001” if less than 0.001. In the summary tables, the mean and median will be presented to 1 more decimal placed than recorded in the data, and standard deviations and standard errors will be reported to 2 more decimal places than recorded in the data; a maximum of 3 decimals places will be reported unless more decimal places are needed to interpret the data.

#### 12.1.4 Computing Environment

All data management and statistical analyses will be performed on Oracle<sup>™</sup>, OracleClinical<sup>™</sup>, ClinTrace<sup>™</sup>, SAS<sup>®</sup>, and S-PLUS<sup>®</sup>.

## 12.2 Efficacy Analysis

Unless otherwise specified, the efficacy analysis will be performed on the ITT population. An analysis using the Per-Protocol population will be performed if the number of patients in the Per-Protocol population is less than 80% of the number of patients in the ITT population.

### 12.2.1 Primary Efficacy Analysis

The primary efficacy analysis will be based on a repeated measures ANCOVA that will be used to test for differences in treatment efficacy between Synvisc and Placebo, as quantified by the WOMAC Subscale A. The primary efficacy hypothesis test will compare the mean change from Baseline over 26 weeks between the two treatment groups. The description of the repeated measures ANCOVA that will be fitted to the data and the statistical inference that will be generated is as follows:

**Model:** The WOMAC Subscale A outcome vector for each patient will consist of the change from baseline to each post-baseline measurement. The outcome vector will be modeled with a repeated measures analysis of covariance model that will include terms for treatment, site, time and time-by-treatment interaction, as well as the baseline WOMAC Subscale A score as a covariate. Based on previous studies of viscosupplementation, the longitudinal response profile of the Synvisc and the Placebo treatment groups are expected to be nonlinear (Caborn et al., 2004, *J Rheumatol*; Day et al., 2004, *J Rheumatol*). Therefore, the analysis will allow for arbitrary patterns in the mean response over time by entering time as a factor variable. The allowable values for time will be the pre-specified visits. Time will also be interacted with treatment to create a time-by-treatment interaction effect. Site will also be included as a factor variable. Sites with less than 4 patients randomized will be pooled into a single category.

The marginal variance-covariance matrix of the outcome vector for a patient will be modeled using an unstructured covariance matrix. The outcomes between patients are assumed to be independent. The model will be fit using maximum likelihood estimation in the PROC MIXED procedure in SAS. An example of the SAS code is provided below (note time is modeled with the visit variable):

#### SAS Display 1 Code for Continuous Endpoints

```
proc mixed data = data method = ml;
  class patid randgrp site visit;
  model y_chg = site baseline randgrp visit visit*randgrp / s;
  repeated visit / type = un subject = patid r;
  where visit > 3;
  lsmeans randgrp randgrp*visit / diff at baseline=overall_baseline_average;
```

**Hypothesis testing and estimation:** The primary efficacy test will be based on a single degree of freedom contrast. The contrast will compare the mean change from Baseline over 26 weeks. Let  $\delta_{over}$  be the difference in the mean change from Baseline over 26 weeks between the Synvisc and Placebo treatment groups. Tests of the difference between Synvisc and Placebo at each of the post-baseline visits will be performed using the least squares means. The above model will also be applied to the observed post-baseline values in order to provide estimates of treatment effects on the observed scale.

### **Figures:**

The following figures will be presented to illustrate the longitudinal trends in the primary efficacy variable:

Estimated longitudinal response profile. Estimates and standard errors of the treatment-specific mean for each scheduled study visit will be generated from the repeated measures ANCOVA of the change from baseline in WOMAC A. The estimated means will be plotted with the associated standard error.

Boxplots of longitudinal response profile. Boxplots of the available data at baseline and each post-baseline study visit will be generated by treatment group. The boxplots will contain a box for the interquartile range (IQR) and a bisecting line for the sample median. The whiskers of the boxplot will extend up to 1.5 IQR from the edges of the box. Data points that reside further than 1.5 IQR from the edges of the box will be denoted with a circle.

## **12.2.2 Supportive Analysis for Primary Efficacy Endpoints**

### **12.2.2.1 Sensitivity Analysis for Missing Data**

No sensitivity analyses are planned as the number of patients with missing data is anticipated to be relatively small.

### **12.2.2.2 Additional Modeling**

**Treatment-by-site interaction:** The assessment of treatment-by-site interaction will be made by fitting an analysis of covariance on the overall average of the WOMAC A. The model will include treatment group, site, a treatment-by-site interaction, and the baseline value as a covariate. Treatment and site will be fixed effects and the analysis will be weighted by the number of observations for which the patient has non-missing values. Least squares means will be presented for each site.

**Treatment-by-country interaction:** The assessment of treatment-by-country interaction will be made by fitting an analysis of covariance on the overall average of the WOMAC A. The model will include treatment group; country; interactions for country by site, country by treatment, and country by site by treatment; and the baseline value as a covariate. Treatment, country, and site

will be fixed effects and the analysis will be weighted by the number of observations for which the patient has non-missing values. Least squares means will be presented for each county.

### 12.2.3 Secondary Efficacy Analyses for Secondary and Tertiary Variables

#### 12.2.3.1 Analysis of Continuous Endpoints

The secondary efficacy analyses will be performed using the repeated measures analysis of covariance model described for the primary efficacy analysis above when the comparisons focus on the observed post-baseline values and the change from Baseline. Estimates of treatment differences and the associated standard errors, 95% confidence intervals and p-values will be generated for each post-baseline efficacy visit and over all visits using the repeated measures ANCOVA.

**Figures:** The figures described for the primary endpoint will be generated for the WOMAC Subscale C , Total WOMAC, and WOMAC Subscale B data.

#### 12.2.3.2 Analysis of Binary Endpoints

Each responder (yes/no) endpoint that is evaluated at multiple post-baseline visits will be analyzed using generalized estimating equations (GEE) for binary outcomes. A GEE model will be fit to the responder data and will include terms for baseline measure, site, visit, treatment group and a visit-by-treatment group interaction. Hypothesis testing will be performed using least squares means based on the linear predictor of the model. An example of the SAS code is displayed below:

#### SAS Display 2 Code for Binary Endpoints

```
proc genmod data = data;  
  class patid site randgrp visit;  
  model response = site baseline visit|randgrp / dist = bin link=logit;  
  repeated subject = patid / within = visit type = unstr corrw;  
  where et_visit > 3;  
  lsmeans randgrp*visit / diff e cl;  
  lsmeans randgrp / diff e cl;  
run;
```

Note that the OMERACT-OARSI endpoint analysis will not have a baseline value. Other responder analyses will use the baseline value of the underlying endpoint (e.g., WOMAC A1 at baseline for the WOMAC A1 responder analysis) as a continuous baseline variable. It is possible that a model can not be fit because of separation or quasi-separation due to the inclusion of the site variable. If this occurs site will be removed from the model.

The WOMAC Subscale A 20% Improvement at Week 26 endpoint will be analyzed using logistic regression.

**Figures:** The percentage of responders at each visit for applicable post-baseline visit for each treatment will be displayed graphically in bar charts for each responder variable: OMERACT-OARSI, WOMAC A1 (Walking Pain), PTGA, COGA, and WOMAC Subscale A at 26 Weeks (responder analysis).

### 12.2.3.3 Analysis of Polytomous Endpoints

Multinomial outcomes will be analyzed using generalized estimating equations (GEE) for a proportional odds logistic regression. The GEE model will be fit to the observed data and will include terms for baseline measure, site, visit, treatment group and a visit-by-treatment group interaction. Hypothesis testing will be performed using estimate statements in Proc Genmod since SAS version 9 will not produce least squares estimates for these models. Due to software constraints an independent working correlation matrix will be used in the analysis, however, standard errors and p-values will reflect the correlations across time because they will use the standard sandwich estimate (Dobson, 2002). An example of the SAS code is displayed below:

#### SAS Display 3 Code for Polytomous Endpoints

```
proc genmod data = data;  
  class patid site randgrp visit;  
  model response = site baseline visit|randgrp / dist = multinomial  
                link=clogit;  
  repeated subject = patid / within = visit ;  
  where et_visid >= ????;  
  estimate 'overall' randgrp <coefficients go here>;  
  estimate 'Week X'  visit*randgrp <coefficients go here>;  
  ...  
  ...  
  ...  
  estimate 'Week Y'  visit*randgrp <coefficients go here>;  
run;
```

**Figures:** A histogram for each treatment at each time will be presented. In each histogram, there will be one bar (or space) for each possible Likert value.

### 12.2.4 Tertiary Efficacy Analysis

#### 12.2.4.1 Use of Rescue Medication

The mean daily consumption of paracetamol over 26 weeks will be presented and analyzed, as will the mean daily consumption of paracetamol between each successive post-baseline visit. The mean daily consumption will be compared at each post-baseline visit between treatment groups using the Wilcoxon Rank Sum test.

In the event that the start and stop dates are not sufficiently complete, the number of patients taking rescue medications over the course of the study will be presented. These data will be tested across treatment groups using the Cochran-Mantel-Haenszel test.

Summaries of the use of rescue medication during the Repeat Treatment Phase will be similar, but will not include any statistical inference.

### **12.2.5 Exploratory Efficacy Analysis**

The following covariates and their interactions with treatment and time will be explored with respect to the change from baseline in WOMAC Subscale A score.

- gender
- age ( $\leq 60$  /  $>60$ )
- lower limb osteoarthritis, where lower limb is defined as hip or contra-lateral knee
- Kellgren-Lawrence Grade in most affected TF compartment
- patello-femoral osteoarthritis, where Kellgren-Lawrence Grades are dichotomized as 0 or I vs. II or III
- tibio-femoral osteoarthritis, where Kellgren-Lawrence Grades are dichotomized as 0, I, or II vs. III
- Kellgren-Lawrence Grades patello-femoral osteoarthritis is  $>$  or  $=$  to Kellgren-Lawrence tibio-femoral osteoarthritis in target knee (yes/no)
- If the number of patients in each category allows it, the patello-femoral Kellgren-Lawrence dichotomy (PF 0 or I, PF II or III) within the tibio-femoral Kellgren-Lawrence dichotomy (TF II, TF III): TF II & PF 0 or I, TFII & PF II or III, TF III &PF 0 or I, TF III &PF II or III.
- effusion at baseline, where presence of effusion at baseline is no for 0-15 ml and yes for  $>15$  ml
- prior viscosupplementation in target knee at baseline (yes/no)
- prior surgery including arthroscopy) of the target knee (yes/no)
- use of any of the following during the study (yes/no): chondroitin sulfate, glucosamine, avocado/soya extracts
- use of chondroitin sulfate during the study (yes/no)
- use of glucosamine during the study (yes/no)
- use of avocado/soya extracts during the study (yes/no)

The effects will be modeled using the repeated measures ANCOVA described above. For each covariate, least square means of the observed WOMAC A score, as well as least square means of the change from baseline in WOMAC A score, will be provided over time by dichotomous level of the covariate. For each covariate, a 3-way interaction term (covariate-by-treatment-by-visit) will be fit in a model along with all 2-way interactions, the main effects, and site and baseline. The least squares means will be generated from the full model.

The p-values of each of the interactions and the covariate also will be provided in the summaries. Generally, if the 3-way interaction is not significant a nominal significance level, then it is removed from the model and the 2-way interactions are explored. However, for the purpose of presenting the p-values in the summaries, the 3-way interaction will be removed from the model that explores the 2-way interactions and all interactions will be removed from the model that generates the covariate p-value.

## **12.3 Safety Analysis**

### **12.3.1 Adverse Events**

Any observed or reported adverse event (AE) that occurs during the study will be recorded on the AE page of the eCRF. AEs manifesting at the time of or after the study treatment will be categorized as treatment-emergent. AEs will be categorized as occurring or not occurring at the target knee and will be summarized and listed separately.

An overall summary table of treatment-emergent AE information will be presented to summarize the frequencies and percentages of patients experiencing one or more of the following: adverse event (AE), treatment-related AE, death, serious adverse event (SAE), discontinuation because of an AE, AE at the target knee, treatment-related target knee AEs (separately for those related to study procedure and those related to study treatment), and target knee SAEs. An overall summary of treatment-emergent local AEs (i.e., AEs of the target knee occurring on the day of injection or on either of the following 2 days and are at least possibly related to study treatment) will be presented; in these summaries, p-values testing treatment differences of the observed rates of each preferred term will be included.

Tables of the events will be presented by system organ class and preferred term (MedDRA) and again by preferred term (sorted by frequency) for all for treatment-emergent AEs. Similar summaries will be presented by severity; if a patient has more than one occurrence of an AE, the most severe occurrence of an AE will be used in the severity summary table. Additional tables will be provided for those adverse events related to injection procedure, and again for those adverse events related to study treatment (i.e., study material). Finally, similar tables of treatment-emergent SAEs will be presented.

All patients who experience treatment-emergent AEs will be listed in Appendix 16, including patient's ID, treatment group, whether the event is related to the target knee, whether the event is

a clinically significant finding from the target knee assessment, system organ class, preferred term, seriousness, severity, relationship to study procedure, relationship to treatment, start and stop dates and times, action taken and outcome. Abbreviated versions of the treatment-emergent adverse events listing will be tabulated separately for the target knee and other sites: (1) for those patients who discontinued due to a treatment-emergent adverse event, and (2) for serious adverse events. A separate listing will be presented in Appendix 16 for patients who experience pre-treatment AEs from the time of informed consent to first study treatment. The format for this listing will be identical to the treatment-emergent AEs except that relationship to treatment will not be included and a variable denoting whether the AE occurred in a washout period will be included.

All the above-mentioned tables and listings, except the listing of pre-treatment adverse events, will be provided for the Safety population; the pre-treatment adverse events listing will be provided for all patients enrolled. Similar tables and listings summarizing those AEs occurring during the Repeat Treatment Phase will be provided for the Repeat Safety population. Treatment-emergent adverse events during the repeat treatment phase will be defined as those events that manifested at the time of or after the repeat phase study treatment.

### **12.3.2 Clinical Laboratory Evaluations**

No laboratory evaluations will be performed for this study.

### **12.3.3 Vital Signs**

The Baseline data, Week 26 data, and change from Baseline to Week 26 will be summarized by treatment group as the number of patients, mean, median, SD, and range. Baseline will be considered the Day 0 vital signs, unless the Day 0 vital signs are missing, in which case the screening vital signs will be considered baseline. A similar table will be presented for the Repeat Treatment Phase, with the change in vital signs calculated as the change from Baseline to Repeat Day 0 and Repeat Week 4, as well as the change from Repeat Day 0 to Repeat Week 4.

### **12.3.4 Physical Examinations**

Changes in the normal/abnormal status of those body systems examined as part of the physical examination will be presented in shift tables. A similar table will be presented for the Repeat Safety population and will consist of the shift from Baseline to Repeat Day 0 and Baseline to Repeat Week 4, as well as a shift from Repeat Day 0 to Repeat Week 4.

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#### 14. APPENDIX 1 ABBREVIATIONS IN THE SAP AND TABLE SHELLS

AE	Adverse event
bpm	Heart beats per minute
C	Degrees centigrade
COGA	Clinical Observer Global Assessment
eCRF	Electronic case report form
ET	Early termination
GEE	Generalised Estimating Equations
HEENT	Head, Ears, Eyes, Nose and Throat
IA	Intra-articular
IQR	Interquartile range (the 75 <sup>th</sup> percentile value minus the 25 <sup>th</sup> percentile value in a distribution of data)
ITT	Intent-to-treat
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	minute
mL	Millilitre
mm	Millimetre
mmHg	Millimetres of mercury
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
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
WHO Drug Dictionary	World Health Organisation Drug Dictionary
WOMAC LK 3.1	Western Ontario and McMaster Universities Osteoarthritis Index Likert Scale Version 3.1