2. SYNOPSIS

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

TITLE OF STUDY:

A Multicenter, Parallel, Double-Blind, Blinded Evaluator, Randomized Comparison of the Efficacy and Safety of an Alternate Viscosupplement (AVS-beta) to Methylprednisolone Acetate in Patients with Symptomatic Osteoarthritis of the Knee

INVESTIGATORS AND STUDY CENTER(S):

Twenty-five sites enrolled patients into this clinical trial. A detailed listing of these sites and the respective Investigators is in the Clinical Study Report.

PUBLICATION (REFERENCE):

No publications have been based on this clinical trial as of yet.

STUDIED PERIOD:

The first patient visit was on 4 October 2004. The last patient visit was on 19 September 2007.

PHASE OF DEVELOPMENT:

Pivotal

OBJECTIVES:

To compare the safety and efficacy of 2x4 mL and 1x4 mL intra-articular (IA) injections of AVS-beta against 1 x 1-mL (40 mg/mL) IA injection of methylprednisolone acetate in treating patients with symptomatic knee osteoarthritis (OA).

METHODOLOGY:

This was a 3-arm multicenter, parallel, double-blind, Blinded Evaluator, randomized clinical study to compare the safety and efficacy of 2 different treatment courses of AVS-beta to methylprednisolone acetate injected into the knee. Patients must have had documented diagnosis of OA of the target knee where the disease had existed for at least 3 months prior to Screening. Patients with bilateral OA of the knees may have been enrolled and had 1 knee treated according to the study protocol, as long as the contralateral (non-study) knee could have been managed by acetaminophen/paracetamol (APAP) alone. Bilateral OA patients with symptomatic OA of the contralateral knee or of the ipsilateral hip that was not responsive to APAP and required other therapy were excluded from this study.

A total of approximately 372 patients were to be randomized in this study. Patient recruitment was not expected to be equal across all participating sites. Initially, 102 patients ("Initial Cohort") were to be randomized at up to 12 North American sites. Enrollment then was to pause to allow the 102 patients to complete up to 8 weeks of follow-up. At that time, an independent Data Monitoring Committee (DMC) was to review relevant safety data from this Initial Cohort, after which, it would make recommendations with regard to further enrollment. The

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

DMC members received data that identified the treatment group assignments but did not identify individual patient treatment assignments. A statistician not involved with the study was responsible for unblinded patient information. The DMC recommended clinical study continuation, and enrollment of the remaining patients continued across all study sites (North America and Europe). Genzyme consulted with the DMC regarding any safety issues on an as-needed basis throughout the duration of the study.

Study Design/Duration:

A period of approximately 36 months was anticipated from the time the first patient was randomized (first patient in) to the completion of the last patient visit (last patient out). Individual patient participation was to last approximately 6 months. If a patient participated in the Repeat Treatment Phase of this study, the duration of his/her participation increased by approximately 6 months. The end of the study was defined as the last patient's last visit.

Screening Phase:

At the Screening visit, patients who agreed to participate underwent the informed consent process. After written informed consent was obtained, a Screening number was assigned and demographic data, height and weight, vital signs, medical history, and prior treatments and medications were obtained. A physical examination and an X-ray with a standing anterioposterior (AP) view of both knees was performed (if an X-ray with a standing AP view of both knees taken within 3 months prior to Screening was not available). If the patient met eligibility criteria, clinical laboratory evaluations for safety (hematology, blood chemistry, and urinalysis) and a serum pregnancy test (for females of childbearing potential) was performed. For patients in the Initial Cohort only, a serum sample for evaluation of antibody response was collected, and a urinalysis was performed, in order to evaluate for an inflammatory response. The patient was instructed to begin the "washout" period of prohibited (pain and OA) medications. The washout period lasted for up to 21 days, depending on the half-life of the medications. Baseline (Day 0) was to be scheduled between 2 and 21 days after Screening to allow for prohibited medication washout, clinical laboratory evaluations results, and patient scheduling. Adverse events (AEs) were collected and recorded from the time the patient signed the informed consent until study completion.

Patients were provided with 500-mg tablets of APAP as rescue medication at Screening and its use was assessed throughout the duration of the trial beginning at Day 0 (Baseline). The maximum dose allowed per day equaled 4000 mg. Therefore, patients may have taken 1 to 2 tablets every 4 to 6 hours as needed (PRN), not to exceed 8 tablets in 24 hours. Rescue medication must not have been used within 48 hours prior to study visits.

Treatment Phase:

The patient's eligibility for participation in the study was re-evaluated at Baseline (Day 0). It was confirmed that the patient still met Screening eligibility criteria and that he/she adhered to the washout period. Adverse events were recorded and any new medical findings and changes in medications or treatments were documented. The patient completed patient questionnaires at Baseline (Western Ontario and McMaster Universities Osteoarthritis Index Likert version 3.1 [WOMAC LK 3.1], patient global assessment [PTGA] and the Health Status Survey, Short Form-36 [SF-36] version 2), and the Blinded Evaluator completed the clinical observer

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

global assessment (COGA). The same Blinded Evaluator was to complete the COGA for a patient throughout the study. A score of 2 or 3 on the WOMAC LK 3.1 A1 (walking pain) and a mean score of 1.5 to 3.5 on the WOMAC LK 3.1 A (pain) was required to qualify for the study.

Using an Interactive Voice Response System (IVRS), the patient was randomized to 1 of 3 treatment groups:

1x4 mL AVS-beta Group: Arthrocentesis followed by a 4-mL IA injection of AVS-beta on Day 0. Arthrocentesis alone at Week 2 (to maintain the treatment blinding).

2x4 mL AVS-beta Group: Arthrocentesis followed by a 4-mL IA injection of AVS-beta on both Day 0 and Week 2.

Steroid Group: Arthrocentesis followed by a 1-mL (40 mg/mL) IA injection of methylprednisolone acetate on Day 0. Arthrocentesis alone at Week 2 (to maintain the treatment blinding).

Patients were monitored for safety during the treatment phase by blinded site personnel. The evaluator and the patient were blinded to the treatment group assignment. Unblinded site personnel, such as the Unblinded Injector, were instructed not to reveal treatment group assignments to blinded personnel or to the patient to ensure that the blinding remained intact. Both study treatment administrations were to occur within the specified window (Table 9-5), 2 weeks apart (Day 0 and Week 2). It was recommended that both injections be administered by the same injector, using the same approach if medically possible.

Follow-up Phase:

All patients were to return for follow-up within specified visit windows at 4, 8, 12, 16, 20 and 26 weeks following the first injection. Safety and efficacy were assessed at each patient visit according to the Schedule of Study Events (Table 9-3). Efficacy assessments included the WOMAC LK 3.1, PTGA, SF-36, and COGA questionnaires, and a pill count of rescue medication. Safety assessments included recording physical examination findings, serum pregnancy test results (for females of childbearing potential), clinical laboratory evaluations results, concomitant medications and treatments, vital signs, and AEs. For patients in the Initial Cohort only, serum samples for evaluation of antibody response were collected at Weeks 4 and 8, and urinalyses were performed in order to evaluate for an inflammatory response. At Week 4, all patients answered a question indicating the treatment that he/she believes that he/she received.

Repeat Treatment Phase:

After completion of all safety and efficacy assessments at the Week 26 visit, patients were offered participation in the Repeat Treatment Phase of the study, which lasted for an additional 6 months. During this visit, the Repeat Treatment Phase inclusion criteria were assessed to determine whether the patient was eligible to receive a course of AVS-beta therapy. Should the patient have met these criteria, an injection visit was scheduled after clinical laboratory evaluations results were available (not more than 7 days after receipt). For the Initial Cohort patients receiving AVS-beta administration during the Repeat Treatment Phase (not for patients followed for safety only), a serum sample for evaluation of antibody response was collected, and a urinalysis was performed at Repeat Weeks 4, 8 and 26, in order to evaluate for an inflammatory response. Urinalyses and antibodies to streptococcal antigens for evaluation of an inflammatory response were not performed on repeat treatment

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

patients who were not part of the Initial Cohort.

Patients entering the Repeat Treatment Phase who were previously randomized to methylprednisolone acetate were re-randomized to 1 of the AVS-beta treatment arms. Patients who were initially randomized to an AVS-beta treatment arm during the first 26 weeks of treatment remained in that same AVS-beta treatment arm.

The Repeat Treatment Phase visit schedule and assessment collection mirrored that of the first 26 weeks of the study (with the exception of the patient assessment of treatment assignment question): treatment consisting of 2 visits as described above and follow-up for efficacy and safety at Repeat Weeks 4, 8, 12, 16, 20 and 26. Rescue medication for the target knee consisted of APAP (not to exceed 4000 mg/day) and was not to be taken within 48 hours prior to study visits.

Patients who did not meet eligibility criteria or who chose not to receive treatment administration were asked to be followed for safety and efficacy during the Repeat Treatment Phase for an additional 26 weeks. Should the patient have agreed to participate, the first follow-up visit was to be scheduled at Repeat Week 4 and the patient was to return for subsequent repeat follow-up visits according to the same schedule as described above.

Patients were 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 have been discontinued at the discretion of the Investigator or Sponsor at any time.

Permitted Treatments and/or Medications:

The following concomitant treatments and/or medications were permitted:

- Any treatment for a pre-existing condition or for an AE, outside of the study indication, that was not listed as prohibited
- Rescue medication (APAP up to 4000 mg/day) for relief of target knee OA pain
  Patients were instructed to discontinue use 48 hours prior to a study visit. Patients were instructed not to take medications (other than provided rescue medications) for target knee pain relief.
- Low-dose aspirin (ASA), 325 mg or less per day, or other platelet aggregation inhibitors (e.g., clopidogrel)
- Other analgesics and analgesic doses of short-acting non-steroidal anti-inflammatory drugs (NSAIDs) for indications other than OA at the target knee, but not for more than 5 consecutive days or 10 days per month, and not within 48 hours prior to a study visit
- 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 (e.g., physical therapy) for the lower extremities, if begun at least 1 month before Screening
  New nonpharmacologic therapy was not to be initiated during the study.

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

- 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
- 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

Prohibited Treatments and/or Medications:

The following concomitant treatments and/or medications were prohibited:

- Analgesics or NSAIDs other than as described in permitted treatments (e.g., rescue medications were not allowed within 48 hours prior to a study visit)
- Chronic use of narcotics
- Systemic corticosteroid(s) (oral or injected)
- IA or periarticular corticosteroid injection (except as required by the protocol) into any joint 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 used within 3 months prior to Screening and during the study (other than as required by the protocol)

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

Three hundred seventy-two patients (124/group) were planned to be enrolled in this study.

The actual number of patients analyzed during the Initial Treatment Phase of the study was 391 patients (2x4 mL AVS-beta: n=129, 1x4 mL AVS-beta: n=130, Steroid: n=132) for the Intent-to-Treat (ITT) Population, and 390 patients (2x4 mL AVS-beta: 124, 1x4 mL AVS-beta: 135, Steroid: 131) for the Safety Population.

During the Repeat Treatment Phase of the study, the Repeat ITT Population consisted of 201 patients (2x4 mL AVS-beta: n=66, 1x4 mL AVS-beta: n=61, Steroid-2x4 mL AVS-beta: n=39, Steroid-1x4 mL AVS-beta: n=35). The Extended Safety Follow-Up Population included 12 patients (2x4 mL AVS-beta: n=3, 1x4 mL AVS-beta: n=7, Steroid-2x4 mL AVS-beta: n=2), and the Repeat Safety Population included 201 patients (2x4 mL AVS-beta: n=66, 1x4 mL AVS-beta: n=61, Steroid-2x4 mL AVS-beta: n=39, Steroid-1x4 mL AVS-beta: n=35).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

INCLUSION:

A patient may have been enrolled in this study if he/she met all of the following criteria:

Screening:

1. Provided signed written informed consent
2. Was able to read and understand the language and content of the study material, understand the requirements for follow-up visits, and was willing to provide information at the scheduled evaluations
3. Was a male or female patient aged 40 years or older
4. Was ambulatory (assistive devices were allowed if used 3 months or more prior to Screening) with an active lifestyle and in good general health
5. Had documented diagnosis of OA of the target knee where the disease had existed for at least 3 months prior to Screening
   Radiographic evidence of OA of the target knee (e.g., presence of osteophytes) at Screening was considered adequate documentation.
6. Met American College of Rheumatology (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 ≤ 30 minutes in duration, and
   - Crepitus on active joint motion

   OR

   - Knee pain for most days of prior month, and
   - Age ≥ 40 years, and
   - Morning stiffness ≤ 30 minutes in duration, and
   - Crepitus on active joint motion
7. Had continued target knee OA pain despite conservative treatment (e.g., weight reduction, physical therapy, analgesics)
8. Was 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)
9. Was willing to discontinue prohibited treatments and medications throughout the study

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

duration

10. Was willing to withhold intake of pain medications for 48 hours prior to all study visits

Baseline:

11. If female, must have had a negative serum pregnancy test (at Screening) and used a medically acceptable form of contraception for at least 1 month prior to Screening and continued use for the duration of the study
    Otherwise, females must have been surgically sterile, or postmenopausal (as documented in medical history) for at least 1 year.
12. Continued to meet all Screening inclusion/exclusion criteria
13. Had completed the pain and OA medication washout period
14. Had pain in the target knee as demonstrated by a score of 2 or 3 on the WOMAC LK 3.1 A1
15. Had a mean score of 1.5 to 3.5 on the WOMAC LK 3.1 A at Baseline (Day 0)

EXCLUSION:

Exclusion Criteria:

A patient was excluded from this study if he/she did not meet the specific inclusion criteria, or if he/she is/had:

1. Modified Kellgren-Lawrence Numerical Grading System of Grade 0 or Grade IV for the target knee confirmed by radiographs performed within 3 months prior to Screening (see definitions below):
   (0) None: No features of OA
   (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. Acute disease or trauma leading to secondary OA of the target knee within 10 years prior to Screening
5. Viscosupplementation in any joint including the target knee within 12 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 on the target knee throughout the duration of the study
   NOTE: Patients who had planned surgery other than for the target knee may have been allowed to participate, if they remained ambulatory and did not use prohibited medications,

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

and if the planned surgery was not anticipated to impact the target knee efficacy assessments.

7. Received physical therapy (at an outpatient/clinic setting) for the target knee that was initiated within 1 month before Screening
8. History of septic arthritis in any joint
9. Concomitant inflammatory disease or other condition that affected 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. Used protocol-prohibited medication/treatments for chronic pain that patient could not have been withdrawn from prior to study treatment at Baseline and throughout the duration of the study
13. Any musculoskeletal condition that would have impeded measurement of efficacy at the target knee
14. Symptomatic OA of the contralateral knee or of the ipsilateral hip, or symptomatic patello-femoral OA of the target knee, that was not responsive to APAP and required other therapy
15. Systemic, or IA injection of corticosteroids in any joint within 3 months prior to Screening
16. Active infection, or history of an infection within the past 12 months, in the area to be injected
17. Any significant chronic skin disorder that could have interfered with evaluation of the injection site
18. Heparin or anti-vitamin K (e.g., crystalline warfarin) anticoagulant therapy
19. Any known contraindication to APAP
20. Any known contraindication to IA corticosteroids
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 have required periodic treatment with systemic steroids during the study period (NOTE: inhaled steroids for this condition were 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 felt would interfere with study evaluations and study participation

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

26. Used an investigational drug, device, or biologic within 3 months before Screening
27. Females who were 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
29. Hypersensitivity to hyaluronan or its derivatives

Repeat Treatment Phase Inclusion Criteria:

Patients who completed the Week 26 assessments may have been enrolled in the Repeat Treatment Phase of this study. In order to receive AVS-beta treatment during the Repeat Treatment Phase, patients were required to meet all of the following criteria:

1. Must have continued to meet Screening inclusion/exclusion criteria
2. Must have had a favorable clinical response to the initial course of treatment defined as a 1-point decrease at some time point from Baseline (Day 0) to Week 26 in the WOMAC LK 3.1 A1 score for the target knee
3. Must have had no major safety concerns during the first course of treatment as assessed by the Investigator
4. Must have had a WOMAC LK 3.1 A1 score of at least 1, and, in the Investigator's clinical assessment, the patient was a candidate for treatment

Patients who did not meet the eligibility criteria listed above or who did not choose to receive AVS-beta treatment administration were asked to be followed for safety and efficacy during the Repeat Treatment Phase for an additional 26 weeks. These patients were grouped as the "Extended Safety Follow-Up Population."

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

Test Product: AVS-beta

Dose:

1x4 mL AVS-beta Group: 4-mL IA injection of AVS-beta on Day 0

2x4 mL AVS-beta Group: 4-mL IA injection of AVS-beta on both Day 0 and Week 2.

Mode of Administration: IA injection

Batch Number(s): [redacted]

DURATION OF TREATMENT:

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

The Initial Cohort (102 patients) enrollment period was approximately 12 months and the enrollment period for the remaining patients took approximately 9 months. However, there was a pause in enrollment (before enrolling the remaining patients) to evaluate the safety data from the Initial Cohort. Patient participation included a 2- to 21-day washout of previous OA and pain medications for target knee OA, 2 visits (Day 0 and Week 2) for study treatment administration, 5 follow-up visits (Weeks 4, 8, 12, 16, and Week 20), and a final study visit (Week 26). If a patient participated in the Repeat Treatment Phase of this study, the duration of his/her participation increased by approximately 6 months.

The end of the study was defined as the last patient's last visit.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

Reference Therapy: methylprednisolone acetate

Dose: Steroid Group: 1-mL (40 mg/mL) of methylprednisolone acetate on Day 0.

Mode of Administration: IA injection

Batch Number(s): [redacted]

CRITERIA FOR EVALUATION:

EFFICACY:

Primary Efficacy Objective

The primary objective of this study was:

- To demonstrate that 2x4 mL injections of AVS-beta provide superior pain relief (WOMAC LK 3.1 A) over 26 weeks as compared to a course of methylprednisolone acetate in treating patients with symptomatic knee OA

If a statistically significant difference was observed with the comparison between the 2 x 4-mL dose versus methylprednisolone acetate at the 5% significance level, then the comparison between the 1 x 4-mL dose versus methylprednisolone acetate would be tested for the primary endpoint.

Secondary Efficacy Variables

The secondary efficacy variables of this study were:

- The positive response to treatment for symptomatic knee OA (where positive response was defined with the Outcomes Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International [OMERACT-OARSI set of criteria) over 26 weeks in the AVS-beta treatment groups and the methylprednisolone acetate group
- The differences between the PTGA over 26 weeks in the AVS-beta treatment groups and the methylprednisolone acetate group

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

- The differences between the WOMAC LK 3.1 A1 over 26 weeks in the AVS beta treatment groups and the methylprednisolone acetate group
- The differences between the COGA over 26 weeks in the AVS-beta treatment groups and the methylprednisolone acetate group

Tertiary Efficacy Variables

The tertiary efficacy variables of this study were:

- The differences between the WOMAC LK 3.1 A change from Baseline to each post-Baseline assessment in the AVS-beta treatment groups and the methylprednisolone acetate group
- The differences between the WOMAC LK 3.1 C (physical function) over 26 weeks and from Baseline to each post-Baseline assessment in the AVS-beta treatment groups and the methylprednisolone acetate group
- The differences between the positive response to treatment for symptomatic knee OA (where positive response was defined with the OMERACT-OARSI [Pham, 2003, *J Rheumatol*] set of criteria) from Baseline to each post-Baseline assessment in the AVS-beta treatment groups and the methylprednisolone acetate group
- The differences between the PTGA change from Baseline to each post-Baseline assessment in the AVS-beta treatment groups and the methylprednisolone acetate group
- The differences between the WOMAC LK 3.1 A1 change from Baseline to each post-Baseline assessment in the AVS-beta treatment groups and the methylprednisolone acetate group
- The differences between the COGA change from Baseline to each post-Baseline assessment in the AVS-beta treatment groups and the methylprednisolone acetate group
- The differences between the Total WOMAC LK 3.1 over 26 weeks and from Baseline to each post-Baseline assessment in the AVS-beta treatment groups and the methylprednisolone acetate group
- The proportions of patients who had a 1-category improvement from Baseline in WOMAC LK 3.1 A over 26 weeks and at each post-Baseline assessment between the AVS-beta treatment groups and the methylprednisolone acetate group
- The change from Baseline in the SF-36 total and subscales over 26 weeks and at each post-Baseline assessment between the AVS-beta treatment groups and the methylprednisolone acetate group
- The use of rescue medication (APAP) over 26 weeks and at each post-Baseline assessment for the AVS-beta treatment groups and the methylprednisolone acetate group

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

Repeat Treatment Phase Efficacy Variables

For the Repeat Treatment Phase of the study, the data were summarized by repeat treatment group. The Repeat Treatment Phase efficacy variables were the changes within each repeat treatment group for: a) the change from Baseline to all Repeat Treatment Phase visits, and b) the change from Repeat Day 0 to all Repeat Treatment Phase visits, for the WOMAC LK 3.1 A1, A and C; the PTGA; the COGA; and the SF-36 total and subscales. The use of rescue medication (APAP) at each scheduled Repeat Treatment Phase visit was summarized.

Data for patients followed but not treated during the Repeat Treatment Phase were listed.

SAFETY:

Safety was determined using the incidence of treatment-emergent AEs, clinical laboratory evaluations, vital signs, and physical examination findings. Adverse events were categorized using a standardized coding dictionary (e.g., Medical Dictionary for Regulatory Activities [MedDRA]). Potential antibody response was evaluated for patients in the Initial Cohort only.

STATISTICAL METHODS:

EFFICACY:

The primary efficacy analysis was performed on the ITT Population, which included all patients randomized. The 2x4 mL AVS-beta treatment group was tested first; if the 2x4 mL dose was significant at the 0.05 level, then the 1x4 mL AVS-beta treatment group was tested. This analysis was based on a repeated measures analysis of covariance (ANCOVA) model that was used to test for differences in treatment efficacy, as quantified by the WOMAC LK 3.1 A over 26 weeks between the AVS-beta treatment groups and the methylprednisolone acetate group. The model included terms for treatment, center, time, time-by-treatment interaction and other relevant covariates such as bilateral knee OA at Baseline. Kellgren-Lawrence Grade at Baseline and the interaction of Kellgren-Lawrence Grade at Baseline and treatment group was included in the model. The primary efficacy objective was tested with functions of the least-square mean estimates of the time-by-treatment combinations.

As with the primary efficacy analysis, the secondary efficacy analyses were performed on the ITT Population. The OMERACT-OARSI responder analysis was analyzed in a model similar to that used for the primary endpoint but appropriate for a binary response variable. In this analysis, patients who had no post-Baseline WOMAC LK 3.1 A, WOMAC LK 3.1 C, and PTGA data were excluded. If a large proportion of patients (i.e., ≥ 10%) had no post-Baseline WOMAC LK 3.1 A, WOMAC LK 3.1 C, and PTGA data, the analysis was repeated including these patients as non-responders.

For the analysis of the odds of positive response over the course of 26 weeks of follow-up, generalized estimating equations (GEEs) were used. Using the Baseline and follow-up data, patients were defined as responders or non-responders at each post-Baseline efficacy visit based on the OMERACT-OARSI set of criteria ([redacted]). The repeated binary outcomes (response, non-response) were used in the GEEs with covariates for treatment group assignments and relevant baseline

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

measures. Wald tests were used to test for the significance of the odds ratio between the 2x4 mL AVS-beta and methylprednisolone acetate groups and between the 1x4 mL AVS-beta and methylprednisolone acetate groups using the empirical variance-covariance matrix.

For the analysis based on the OMERACT-OARSI criteria, patients who discontinued the study prior to the Week 26 assessment due to either target knee-related AEs or due to lack of efficacy were classified as non-responders in the efficacy analysis. No replacement of any other missing or invalid data was made for this analysis. Kellgren-Lawrence Grade at Baseline and the interaction of Kellgren-Lawrence Grade at Baseline and treatment group were included in model.

The PTGA, WOMAC LK 3.1 A1, and COGA data were analyzed over 26 weeks and at each post-Baseline visit using proportional odds logistic regression. While the measure used for the primary efficacy analysis was an average of scores that comprise the WOMAC LK 3.1 A subsection, these endpoints each consisted of 1 question measured on the Likert scale and, therefore, do not exhibit the requisite properties for an analysis of variance. The proportional odds logistic regression model was designed to handle distributions of categorical data such as the Likert scale and could be extended to the repeated-measures design through GEEs.

The odds of positive response to treatment for symptomatic knee OA with a 2x4 mL and/or 1x4 mL IA injections of AVS-beta compared to patients treated with a course of methylprednisolone acetate at each post-Baseline efficacy visit was modeled with logistic regression that included covariates for treatment group assignments and relevant baseline measures. The modeling of the odds of positive response from each post-Baseline efficacy visit to the final post-Baseline efficacy visit was modeled with GEEs as outlined for the analysis of OMERACT-OARSI.

Repeated measures ANCOVA was used for the analysis of the WOMAC LK 3.1 A change from Baseline to each post-Baseline visit, and the WOMAC LK 3.1 C and Total WOMAC LK 3.1 changes over 26 weeks and from Baseline to each post-Baseline visit. Estimates of the change from Baseline to each post-Baseline visit were used to test the tertiary efficacy hypotheses when a repeated measures model was used. Estimates of the mean difference over all of the study visits were used to test the tertiary efficacy hypotheses of overall difference for WOMAC LK 3.1 C and Total WOMAC LK 3.1.

In addition, tables summarizing the response variables, including the sample size, mean, median, standard deviation (SD), and range, are presented.

Patients were defined as responders if they had a 1-category improvement from Baseline in WOMAC LK 3.1 A at each post-Baseline assessment. These data were analyzed over 26 weeks and at each post-Baseline assessment. The proportion of responders are presented for each treatment group and compared between the AVS-beta treatment groups and the methylprednisolone acetate group using logistic regression.

The change over 26 weeks and at each post-Baseline assessment in the SF-36 total and subscales between the AVS-beta treatment groups and the methylprednisolone acetate group were analyzed with simplified versions of the ANCOVA model used for the primary model because SF-36 was only collected at Weeks 12 and 26.

The comparison of rescue medication pill counts was made between the AVS-beta treatment groups and the

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

methylprednisolone acetate group over 26 weeks and at each post-Baseline assessment via 2-sample t-tests.

Efficacy analyses were repeated on the Per-Protocol Population, which excluded all patients with major protocol violations.

Repeat Treatment Phase

For the Repeat Treatment Phase of the study the data were summarized by repeat treatment group. The data were summarized using descriptive statistics for Initial Cohort patients and for all patients enrolled in the Repeat Treatment Phase. Tables summarizing the response variables, including the sample size, mean, median, SD, range, and 95% confidence interval (CI) are presented. No formal statistical tests were performed on data collected during the Repeat Treatment Phase of the study.

Power and Sample Size:

Approximately 372 patients with symptomatic knee OA were to be randomized. Assuming a dropout rate of 15% and a 2-sided significance level of 5% for the primary efficacy endpoint, this sample size provided over 80% power to detect an overall difference of 0.32 in the change from Baseline WOMAC LK 3.1 A (assuming a common SD of 0.74) between the AVS-beta treatment groups and the methylprednisolone acetate group over the course of 26 weeks.

The power calculation for the WOMAC LK 3.1 A assumed that a 2-sample t-test comparing the within-treatment group means of the patient-specific mean change from Baseline was used. The 2-sample t-test approximates tests of the null hypotheses based on the repeated measures model that was used in the primary efficacy analysis.

The assumptions of a common SD of 0.74 and overall difference of 0.32 were also based on the results of Genzyme/Wyeth Study Number 901 ([redacted]). The overall difference of 0.32 is a function of the different longitudinal response profiles of IA corticosteroid treatment and viscosupplementation. The differences are small in the early stages of post-treatment due to the rapid but short-lived pain relief from corticosteroids and progressive effectiveness of viscosupplementation. The differences between viscosupplementation and corticosteroids tend 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. ([redacted]).

Assuming a dropout rate of 15% and a 2-sided significance level of 5% for the OMERACT-OARSI efficacy endpoint, this sample size provided over 90% power to detect an odds ratio of 0.42 for the OMERACT-OARSI response rate between the AVS-beta treatment groups and the methylprednisolone acetate group over the course of 26 weeks.

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

SAFETY:

The safety analyses were performed on the Safety Population defined as all patients who underwent the first injection. Treatment-emergent AEs were summarized by treatment group and categorized by severity and relationship to the study procedures or treatments. Treatment-emergent AEs were summarized both by inclusion and exclusion of AEs generated from deteriorations noted in the target knee assessment. Target knee AEs also were summarized separately. Additionally listings of serious AEs (SAEs) and AEs leading to discontinuation were generated.

Clinical laboratory evaluations, vital signs and physical examination findings were tabulated. Concomitant medications and treatments were summarized. For the Repeat Treatment Phase of the study, all treatment-emergent AEs were summarized by treatment group for the Repeat Safety Population.

RESULTS:

Primary Efficacy

The Baseline mean WOMAC LK 3.1 A (pain) score was 2.24 (SD 0.403) for the 2x4 mL AVS-beta group, 2.24 (SD 0.411) for the 1x4 mL AVS-beta group, and 2.21 (SD 0.400) for the Steroid group. The estimated change from Baseline over 26 weeks was -0.86 (standard error [SE] 0.064) in the 2x4 mL AVS-beta group, -0.81 (SE 0.058) in the 1x4 mL AVS-beta group, and -0.91 (SE 0.058) in the Steroid group. Within-group changes from Baseline over 26 weeks were statistically significant ($p<0.0001$). The estimated treatment differences between the 2 treatment groups and Steroid over the 26-week study (2x4 mL AVS-beta: 0.05 [SE 0.084], 1x4 mL AVS-beta: 0.11 [SE 0.078]) were not statistically significant.

For the ITT Population, the overall estimated WOMAC LK 3.1 A (pain) score for patients with Kellgren-Lawrence Grades I or II was 1.39 for the 2x4 mL AVS-beta group, 1.48 for the 1x4 mL AVS-beta group, and 1.20 for the Steroid group; the estimated change from Baseline was -0.84 for the 2x4 mL AVS-beta group, -0.76 for the 1x4 mL AVS-beta group, and -1.03 for the Steroid group; a difference of 0.19 ($p=0.1802$) for the 2x4 mL AVS-beta group, and 0.27 ($p=0.0287$) for the 1x4 mL AVS-beta group in favor of Steroid. The overall estimated WOMAC LK 3.1 A (pain) score for patients with Kellgren-Lawrence Grade III was 1.35 for the 2x4 mL AVS-beta group, 1.37 for the 1x4 mL AVS-beta group, and 1.43 for the Steroid group; the estimated change from Baseline was -0.88 for the 2x4 mL AVS-beta group, -0.86 for the 1x4 mL AVS-beta group, and -0.80 for the Steroid group; a difference of -0.08 ($p=0.3742$) for the 2x4 mL AVS-beta group, and -0.06 ($p=0.5482$) for the 1x4 mL AVS-beta group in favor of AVS-beta. In summary, the treatment effect observed for both AVS-beta treatment groups was similar for patients across the Kellgren-Lawrence Grades. In contrast, Steroid seemed to perform worse in patients with Kellgren-Lawrence Grade III than in those with Kellgren-Lawrence Grades I or II.

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

Secondary Efficacy

For the ITT Population, 56.6% of patients in the 2x4 mL AVS-beta group, 49.2% of patients in the 1x4 mL AVS-beta group, and 50.0% of patients in the Steroid group were classified as OMERACT-OARSI Responders at Week 26. The majority of patients' PTGA and COGA ratings improved from poor or fair at Baseline to fair, well or very well at Week 26. The majority of patients experienced moderate or severe walking pain (WOMAC LK 3.1 A1) at Baseline that improved to moderate or mild walking pain at Week 26. Within treatment groups, mean PTGA, COGA and WOMAC LK 3.1 A1 scores improved from Baseline to Week 26 for all patients. However the differences between the AVS-beta treatment groups and the Steroid group overall were not statistically significant.

Repeat Treatment Phase Efficacy

For the Repeat ITT Population, mean WOMAC LK 3.1 A1, WOMAC LK 3.1 A, WOMAC LK 3.1 C, PTGA and COGA scores improved from Baseline and from Repeat Day 0 to Repeat Week 26 for patients in all treatment groups.

There were statistically significant ($p<0.0001$) within-group changes from Baseline to Repeat Week 26 in WOMAC LK 3.1 A1 (2x4 mL AVS-beta: -1.1, SD 0.88; 1x4 mL AVS-beta : -1.0; SD 0.86), WOMAC LK 3.1 A (2x4 mL AVS-beta: -1.07, SD 0.648; 1x4 mL AVS-beta: -0.96, SD 0.747), WOMAC LK 3.1 C (2x4 mL AVS-beta: -0.95, SD 0.655; 1x4 mL AVS-beta : -0.91; SD 0.744), PTGA (2x4 mL AVS-beta: -1.1, SD 0.99; 1x4 mL AVS-beta : -0.9; SD 0.92), and COGA (2x4 mL AVS-beta: -1.1, SD 1.13; 1x4 mL AVS-beta: -1.4; SD 1.02).

Statistically significant within-group changes from Repeat Day 0 to Repeat Week 26 occurred in the WOMAC LK 3.1 A1 (2x4 mL AVS-beta : -0.4, SD 0.80, $p<0.0001$), WOMAC LK 3.1 A (2x4 mL AVS-beta: -0.37, SD 0.677, $p=0.0002$; 1x4 mL AVS-beta: -0.27, SD 0.724, $p=0.0063$), WOMAC LK 3.1 C (2x4 mL AVS-beta: -0.27, SD 0.594, $p=0.0011$; 1x4 mL AVS-beta: -0.27, SD 0.668, $p=0.0045$), PTGA (2x4 mL AVS-beta: -0.3, SD 0.86, $p=0.0104$), and COGA (1x4 mL AVS-beta -0.4, SD 1.00, $p=0.0068$).

Within-group changes from Baseline for SF-36 physical component scores were statistically significant ($p<0.0001$) at Repeat Week 26 (2x4 mL AVS-beta: 7.42; SD 8.298; 95% CI 4.90, 10.81; 1x4 mL AVS-beta: 6.48; SD 6.638; 95% CI 2.81, 9.20). Within-group changes from Repeat Day 0 for physical component scores also were statistically significant at Repeat Week 26 (2x4 mL AVS-beta: 2.29; SD 6.351; 95% CI 0.35, 4.07; $p=0.0142$; 1x4 mL AVS-beta: 1.83; SD 7.244; 95% CI 0.72, 4.30; $p=0.0534$). Within-group changes for SF-36 mental component scores from Baseline to Repeat Week 26 and from Repeat Day 0 to Repeat Week 26 were not statistically significant.

Safety

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

Overall, for the Initial Treatment Phase, 258 of 390 patients (66.2%) experienced at least 1 AE during study conduct (2x4 mL AVS-beta: n=86, 69.4%; 1x4 mL AVS-beta: n=91, 67.4%; Steroid: n=81, 61.8%). Of these, 98 patients (25.1%; 2x4 mL AVS-beta: n=33, 26.6%; 1x4 mL AVS-beta: n=36, 26.7%; Steroid: n=29, 22.1%) had AEs that were considered by the Investigator to be possibly, probably or definitely related to study treatment. Adverse events in the target knee occurred in 159 patients (40.8%; 2x4 mL AVS-beta: n=52, 41.9%; 1x4 mL AVS-beta: n=61, 45.2%; Steroid: n=46, 35.1%). "Other" AEs occurred in 226 patients (57.9%; 2x4 mL AVS-beta: n=73, 58.9%; 1x4 mL AVS-beta: n=77, 57.0%; Steroid: n=76, 58.0%). Eighteen patients (4.6%, 2x4 mL AVS-beta: n=5, 4.0%; 1x4 mL AVS-beta: n=5, 3.7%; Steroid: n=8, 6.1%) experienced at least 1 SAE during study conduct. One death (Steroid: n=1, 0.8%) occurred during the conduct of this study. Twelve patients (3.1%; 1x4 mL AVS-beta: n=5, 3.7%; Steroid: n=7, 5.3%) withdrew from the study due to AE(s), none of which was considered by the Investigator to be related to study treatment (procedure-related and/or treatment-related).

Overall, 126 of 201 patients (62.7%) experienced at least 1 AE during the Repeat Treatment Phase of the study (2x4 mL AVS-beta: n=41, 63.1%; 1x4 mL AVS-beta: n=42, 67.7%; Steroid-2x4 mL AVS-beta: n=24, 60.0%; Steroid-1x4 mL AVS-beta: n=19, 55.9%). Of these, 40 patients (19.9%; 2x4 mL AVS-beta: n=12, 18.5%; 1x4 mL AVS-beta: n=13, 21.0%; Steroid-2x4 mL AVS-beta: n=7, 17.5%; Steroid-1x4 mL AVS-beta: n=8, 23.5%) had AEs that were considered by the Investigator to be possibly, probably or definitely related to study treatment. Adverse events in the target knee occurred in 60 patients (29.9%, 2x4 mL AVS-beta: n=18, 27.7%; 1x4 mL AVS-beta: n=20, 32.3%; Steroid-2x4 mL AVS-beta: n=9, 22.5%; Steroid-1x4 mL AVS-beta: n=13, 38.2%). Of these, 40 patients (19.9%, 2x4 mL AVS-beta: n=12, 18.5%; 1x4 mL AVS-beta: n=13, 21.0%; Steroid-2x4 mL AVS-beta: n=7, 17.5%; Steroid-1x4 mL AVS-beta: n=8, 23.5%) had target knee AEs that were considered by the Investigator to be possibly, probably or definitely related to study treatment. Twenty-nine patients (14.4%, 2x4 mL AVS-beta: n=6, 9.2%; 1x4 mL AVS-beta: n=10, 16.1%; Steroid-2x4 mL AVS-beta: n=6, 15.0%; Steroid-1x4 mL AVS-beta: n=7, 20.6%) had target knee AEs that were considered by the Investigator to be possibly, probably or definitely related to study procedure. Forty-two patients (20.9%, 2x4 mL AVS-beta: n=12, 18.5%; 1x4 mL AVS-beta: n=14, 22.6%; Steroid-2x4 mL AVS-beta: n=7, 17.5%; Steroid-1x4 mL AVS-beta: n=9, 26.5%) had target knee AEs that were considered by the Investigator to be possibly, probably or definitely related to study treatment and/or procedure. There were 2 target knee SAEs during the Repeat Treatment Phase of the study (Patient 08913 in the 1x4 mL AVS-beta group [arthralgia], and Patient 07019 in the Steroid-2x4 mL AVS-beta group [tibia fracture]. A summary of the remaining 5 SAEs are in Table 12-23.

SUMMARY – CONCLUSIONS

[redacted],

NAME OF COMPANY **Genzyme Corporation, Biosurgery** **55 Cambridge Parkway** **Cambridge, MA 02142** **USA** **Genzyme Europe BV** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** NAME OF FINISHED PRODUCT **Alternate Viscosupplement-beta (AVS-beta)** NAME OF ACTIVE INGREDIENT **N/A**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

- The treatment effect (degree and duration) of a single IA injection of 40 mg of methylprednisolone acetate observed in this trial is markedly different than was expected based on the published literature (Caborn, 2004, J Rheumatol.) and the clinical experience with IA corticosteroid use in knee OA.
- The estimated treatment differences for WOMAC LK 3.1 A (pain) between the 2 AVS-beta treatment groups and Steroid over the 26-week study (2x4 mL AVS-beta: 0.05, 1x4 mL AVS-beta: 0.11) were not statistically significant.
- However, within-group changes from Baseline over the study period of 26 weeks were statistically significant for all treatment groups (2x4 mL AVS-beta: -0.86, 1x4 mL AVS-beta: -0.81, Steroid: -0.91; $p<0.0001$).
- The treatment effect observed for both AVS-beta treatment groups was similar for patients across the Kellgren-Lawrence Grades. In contrast, Steroid seemed to perform worse in patients with Kellgren-Lawrence Grade III than in those with Kellgren-Lawrence Grades I or II.
- The overall frequencies of AEs and target knee AEs during the Initial Treatment Phase of the study were comparable between the treatment groups. Target knee AEs occurred at a slightly higher frequency in the AVS-beta groups versus the Steroid group. The type and frequency of treatment-emergent AEs indicate acceptable safety profiles for AVS-beta and for Steroid in the treatment of knee OA over the 6-month course of initial treatment. The safety profile from the Initial Treatment Phase of the study was confirmed during the Repeat Treatment Phase of the study, indicating no increase of AEs in the patients receiving repeat treatment with AVS-beta.
- Repeat treatment with AVS-beta (1 or 2 injections) provides continued pain relief for an additional 26 weeks.