Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

1 SYNOPSIS

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**
TITLE OF STUDY: Study to Evaluate the Dose, Safety and Effectiveness of Recombinant Human Thyroid Stimulating Hormone-Modified (rhTSH-M)[1] When Used In Conjunction with Radioiodine for the Treatment of Multinodular Goiter (MNG)		
INVESTIGATORS: [redacted]		
STUDY CENTRE(S): Patients were enrolled at 13 study sites in the USA (2 sites), EU (7 sites), Canada (2 sites), and Brazil (2 sites) in this study.		
PUBLICATION (REFERENCE): Graf H, Fast S, Pacini F, Pinchera A, Leung A, Vaisman M, et al. Modified-release recombinant human TSH (MRrhTSH) augments the effect of ^{131}I therapy in benign multinodular goiter: Results from a multicenter international, randomized, placebo-controlled study. J Clin Endocrin Metab. 2011; 96(5):1368–1376.		
STUDIED PERIOD: The first patient provided informed consent on 16 July 2007 and the last patient completed the study on 29 July 2011.		
PHASE OF DEVELOPMENT: 2		
BACKGROUND: The Core Study clinical study report (CSR), which presents the description and results, including the primary efficacy analysis, for the first 6 months of the study (hereafter referred to as the "Core Study"), was finalized 24 August 2009. Following the Core Study, the study continued to collect efficacy and safety data until Month 36 for the patients enrolled in this study to evaluate the long-term effects of rhTSH-M as an adjuvant to radioiodine therapy for MNG. This synoptic CSR includes the results of both the Core Study and the Extended Follow-up Phase.		
OBJECTIVES: To determine the dose-response and safety of 2 doses of rhTSH-M with radioiodine (^{131}I) therapy to achieve goiter shrinkage and improve goiter symptoms compared with ^{131}I therapy alone in an adult population with small to moderate-sized MNG.		

[1] rhTSH-M was previously named modified-release recombinant human thyroid stimulating hormone (MRrhTSH). This name will be found in documents (i.e., protocol) and the tables and listings for this study. This synopsis will use rhTSH-M.

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

METHODOLOGY:

This was a Phase 2, randomized, single-blinded, placebo-controlled, 3-arm, parallel group, dose-selection study designed to evaluate the dose, safety, and effectiveness of rhTSH-M when used in conjunction with ^{131}I for the treatment of MNG. This study consists of 2 parts: (1) the first 6 months of the study (Core Study); and (2) an additional 30-month extension phase (hereafter referred to as the "Extended Follow-up Phase") that was incorporated into the protocol under Amendment 4.

Potential study participants were screened for eligibility during Screening Period 1 (SP1) and Screening Period 2 (SP2). After providing signed informed consent, patients underwent a series of initial screening evaluations during SP1 (which were to be completed within 21 days after signing the informed consent form [ICF]) to determine their initial eligibility status. During this time, relevant patient information was collected and then reviewed by the Investigator to determine patient eligibility. Once all SP1 procedures were completed and the results found to meet the appropriate criteria, patients proceeded to complete the SP2 procedures (which were to be completed over a period of 3 weeks [+3 days]). Screening Period 2 assessments were to have commenced no later than 22 days after signing the ICF.

Baseline computerized tomography (CT) scans of the neck were done during SP2 before patients had received any study treatment. The CT scans were evaluated in a blinded manner by an independent reader (expert radiologist) at a centralized reading facility. Thyroid volumes were definitively calculated using a standardized and centralized procedure. Note that if the CT scan-based measurement of a patient's thyroid volume was either greater than the upper thyroid volume (i.e., >140 mL) or less than the lower thyroid volume (i.e., <40 mL) allowed by the study inclusion criteria (see below) measured by ultrasound at SP1, the patient was retained in the study. The baseline goiter volume was calculated centrally using the first CT scan (at SP2) for each patient. The definitive, centrally determined goiter volume was used for the calculation of μCi/g goiter, and thus for the required therapeutic activity of ^{131}I. Smallest cross sectional area of the trachea (SCAT) was evaluated in an analogous manner (i.e., the definitive SCAT value was determined by the central reader). Note that if the baseline SCAT measurement did not meet the study entry criterion (i.e., be $\geq$60 mm^2), the patient was withdrawn from the study prior to Visit 1 and prior to receiving treatment.

Once patients completed all SP1 and SP2 procedures and were determined to meet all entry criteria, they were eligible for randomization. Eligible patients were randomly assigned to treatment with placebo plus ^{131}I (Arm A), a single intramuscular (IM) dose of 0.01 mg rhTSH-M plus ^{131}I (Arm B), or 0.03 mg rhTSH-M plus ^{131}I (Arm C). Patients remained blinded to their treatment, but the Investigator, Sponsor, and study personnel were not blinded to treatment. Following treatment, patients returned for scheduled Core Study follow-up visits and routine safety assessments on Day 1, Day 2, Day 5, Day 14, Day 30, Day 60, Day 90 and Month 6/ET. At Month 6, a CT scan of the neck was performed and evaluated in a blinded manner by an independent reader (expert radiologist) at a centralized reading facility to determine the primary endpoint of the Core Study (goiter volume shrinkage over 6 months).

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

Patients who completed the Core Study and signed a separate informed consent form continued in the Extended Follow-up Phase. The Extended Follow-up Phase was comprised of quarterly study visits, which concluded with a follow-up visit 36 months after Day 0 (i.e., Visit 18). No study drugs (i.e., rhTSH-M or placebo) or other investigational drugs (i.e., Thyrogen) for the treatment of goiter were administered during the Extended Follow-up Phase. Routine safety assessments were performed according to the protocol-defined schedule of study events. At Month 36 (or Early Termination) a final CT scan of the neck and SCAT determination was performed by a blinded central reader, as described above for the Core Study.

Please see Section 16.1.1 for the complete protocol and amendments.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

Planned

A total of 99 patients were to be enrolled and randomized into 3 study arms:

- Arm A: 33 patients to placebo + ^{131}I arm
- Arm B: 33 patients to 0.01 mg rhTSH-M + ^{131}I arm
- Arm C: 33 patients to 0.03 mg rhTSH-M + ^{131}I arm

Analyzed

A total of 141 patients were enrolled (provided signed informed consent) in this study. Of these, 96 patients were randomized; 95 received study drug; 95 patients were included in the Full Analysis Set (FAS), 90 patients were included in the Per Protocol Set (PPS), and 95 patients were included in the Safety Set.

A total of 91 patients entered (provided signed informed consent) the Extended Follow-up Phase; thus 91 patients are included in analyses of the Extended Follow-up Phase.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Patients who met all of the following inclusion criteria were eligible to participate in this study:

1. Adults aged 35 to 80 years old, inclusive.
2. Clinical diagnosis of multinodular goiter, judged clinically and by ultrasound at Screening to be at least 40 mL, but less than or equal to 140 mL in size.
3. Clinically free of thyroid cancer as determined by Fine Needle Aspiration (FNA) of all dominant and/or highly suspicious cold nodules in the goiter and cytology reports as negative for thyroid cancer. (Note: Results of FNA and cytology reports that were performed within 18 months prior to commencing screening procedures and met these criteria were acceptable for inclusion.).
4. Principal Investigator must have believed that there was a minimal risk of coexistent thyroid cancer.

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

5. Principal Investigator felt that the patient's iodine intake and/or levels would not significantly impact the results of the study (a urinary iodine assay at Screening and low-iodine diet were optional and associated data were not collected for study purposes).
6. Baseline serum level of free thyroxine index (FTI) within the normal range, as determined by central lab.
7. Baseline serum level of thyroid stimulating hormone (TSH) ranges from undetectable to the upper limit of the normal range, as determined by central lab.
8. Females of childbearing potential must have been on a stable hormonal contraceptive regimen (i.e., >6 months continuous use) and/or used a double-barrier method (i.e., condom and foam) through Visit 8 (i.e., until the end of the Core Study). Note: In Denmark, the contraceptive method for females of childbearing potential was limited to a stable hormonal contraceptive regimen (i.e., >6 months continuous use).
9. Through Visit 8 (6 months) of a male patient's participation in the study, it was recommended that his sexual partner(s), who were females of childbearing potential, use the methods of contraception described above.
10. Negative pregnancy tests for all women of childbearing potential prior to participating in the study. Women aged 50 years and above and considered postmenopausal (defined as >2 years since last menstrual period) were not required to have a pregnancy test.
11. Routine blood laboratory values within normal range at Screening, as determined by central lab. Abnormal values considered to be not clinically significant by the Principal Investigator were acceptable for inclusion.
12. Electrocardiogram (ECG; 12-lead, 2-minute rhythm strip) within normal limits at Screening as determined by a designated study cardiologist or appropriately qualified physician at each site. Evidence of an old myocardial infarction (MI) excluded a patient. Patients who had ECG findings of occasional premature atrial beats, abnormal PR intervals not associated with supra ventricular tachycardia or heart block, right bundle branch block, and heart rates ≤100 bpm and ≥50 bpm may have been included in the study.
13. Committed to follow all protocol-required study procedures as evidenced by providing written informed consent within 21 days prior to SP2.

Patients who met any of the following <u>exclusion</u> criteria were not eligible for participation in this study:

1. History of thyroid cancer.
2. Previous partial or near total thyroidectomy.
3. Clinical history, signs, or symptoms that made thyroid cancer a higher than usual probability, such as positive immediate family history of thyroid cancer, history of head or neck irradiation, a

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

stone-hard nodule or suspicious growth of a nodule in recent months, palpable cervical lymph nodes, or nodes that on ultrasound have features suspicious for metastases (unless ruled out by biopsy or FNA).

4. During the 45 days before administration of rhTSH-M or placebo (i.e., SP1 and SP2), use of propylthiouracil, methimazole or thyroxine, vitamins or supplements containing kelp or iodine (taking a multivitamin that does not contain iodine or kelp was acceptable), medications that significantly affect iodine handling such as high-dose corticosteroids, high-dose diuretics, or lithium (low- or moderate-dose diuretic use was acceptable). (Note: Details on the allowable doses were included in the Study Operations Manual.)
5. Had currently or within the past 60 days used retinoic acid.
6. Serum calcitonin above the upper limit of normal at Screening, as determined by central lab.
7. Used amiodarone within the prior 2 years.
8. Received iodine-containing contrast agent within the past 3 months.
9. Inability to complete all required visits.
10. Had conditions in which the use of beta-blockers was medically contraindicated, such as recently active asthma or clinically significant chronic obstructive pulmonary disease.
11. Currently or within the past 5 years had a history of malignancy, other than squamous or basal cell carcinoma of the skin or carcinoma *in situ* of the cervix.
12. Prior MI, even if remote; stroke within 6 months; Atrial fibrillation or clinically significant arrhythmia within 6 months (patient may have had mild hypertension or chronic cardiac illnesses that were well-controlled on a medication regimen; blood pressure [BP] less than 140/90 mmHg after resting 5 minutes).
13. A concurrent major medical disorder (e.g., documented significant cardiac disease, debilitating cardiopulmonary disease, advanced renal failure, advanced liver disease, advanced pulmonary disease, or advanced cerebral vascular disorder) that may have had an impact on the capability of the patient to adequately comply with the requirements of this study.
14. Women who were pregnant or lactating.
15. A recent history of alcoholism, drug abuse, or other disorder that may have affected compliance with the protocol.
16. Received investigational study medication within 30 days prior to signing informed consent and/or intended to participate in another clinical study involving the use of an investigational drug over the course of study participation.
17. On anticoagulants, except for aspirin.

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

18. Known at the time of Screening due to past testing to be human immunodeficiency virus (HIV) antibody positive or hepatitis B antigen positive (no screening for HIV or hepatitis B should have been done in the study).
19. Hyperthyroid symptom scale (HSS) ≥20.
20. Had received ^{131}I in the past, and had a lifetime exposure believed to be >10 mCi (0.37 GBq) of ^{131}I.
21. History of allergy to Thyrogen.
22. Sodium carboxymethylcellulose (NaCMC) allergy (including prior history of anaphylaxis following topical lidocaine, barium sulfate ingestion, or intra-articular or parenteral corticosteroid).
23. SCAT discovered on CT to be <60 mm^2.

Extended Follow-up Phase Entry Criteria

Completed the first 6 months of the study (i.e., the Core Study) and signed a separate informed consent form for the Extended Follow-up Phase.

A sample informed consent form for the Extended Follow-up Phase can be found in Appendix 16.1.3.

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

rhTSH-M was administered by a single intramuscular (IM) injection to the buttocks at 1 of the following 2 doses: 0.01 mg and 0.03 mg.

DURATION OF TREATMENT:

A single dose of the investigational study product (either 0.01 mg or 0.03 mg rhTSH-M) or placebo was administered on Day 1.

Twenty-four hours (± 6 hours) after administration of rhTSH-M or placebo, patients also received a therapeutic activity of ^{131}I as a single oral dose.

No study drugs were administered during the Extended Follow-up Phase.

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

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

Radioiodine (^{131}I) served as the standard therapy comparator. Patients randomized to the rhTSH-M treatment groups received a therapeutic activity of ^{131}I as a single oral dose 24 hours (±6 hours) after administration of rhTSH-M. It was intended that no patients should receive >100 mCi ^{131}I as their therapeutic activity in this study.

Patients randomized to the ^{131}I only arm received a placebo injection to the buttocks consisting of 0.5 mL of 3% NaCMC.

CRITERIA FOR EVALUATION:

EFFICACY:

Core Study

Primary endpoint:

- Change from baseline to 6 months in goiter size by CT scan.

Secondary endpoints:

- Change from baseline to 6 months in SCAT.
- Thyroid Quality of Life Questionnaire (ThyQoL).
- TSH, free thyroxine (FT4), total thyroxine (TT4), FTI, free triiodothyronine (FT3), total triiodothyronine (TT3).
- The percentage of patients in each group who attained goiter volume shrinkage at 6 months of 28% or greater.

Tertiary Endpoint:

- Change from baseline measurement to 6 months in goiter size by neck ultrasound.

Extended Follow-up Phase

- Percent change in goiter volume from Baseline (SP2) to Month 36
- Percent change in goiter volume from Month 6 to Month 36
- Percent change in SCAT from Baseline (SP2) to Month 36
- Percent change in SCAT from Month 6 to Month 36
- Differences between treatment groups on the ThyQoL goiter-specific items at Month 12, Month 24, and Month 36
- Change from Baseline (SP2) to Month 12, Month 24, and Month 36 on the ThyQoL goiter-specific items
- Change from Month 6 to Month 12, Month 24, and Month 36 on the ThyQoL goiter-specific items
- Change from Baseline (SP1) to Months 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36/ET for TSH, FT4, TT4, FT3, and TT3

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

- Change from Month 6 to Months 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36/ET for TSH, FT4, TT4, FT3, and TT3
- Percent change in goiter volume measured by ultrasound from Baseline (SP1) to Month 12, Month 24, and Month 36

SAFETY:

- Routine laboratory tests, serial thyroid-function tests (TFTs), antibodies against rhTSH-M, antibodies against the thyroid stimulating hormone receptor (TSHR-Ab; for patients who were hyperthyroid at Visits 6 or 7 only), and physical examinations.
- Tracheal diameter measurements determined by ultrasound at Visit 3 (Day 5) compared to baseline measurement.
- Change in goiter size as measured by ultrasound from baseline measurement to maximum size as measured at Visit 3 (Day 5). (Note that this was a safety endpoint at Visit 3 only, when it was used to assess transient swelling of the thyroid after administration of study treatments at Visits 1 and 2. In all other instances, this was an efficacy endpoint.)
- ECG findings (12-lead, 2-minute rhythm strip) in all patients.
- Respiratory symptoms (directed question).
- Adverse events (AEs) / serious adverse events (SAEs).
- Vital signs.
- Treatment-emergent hyperthyroidism (HSS score ≥20).

STATISTICAL METHODS:

A detailed statistical analysis plan (SAP) for the Core Study and Extended Follow-up Phase was developed prior to completion of patient enrolment in the Core Study.

EFFICACY:

All efficacy analyses were performed on the FAS (comprised of all patients who received 1 dose of the study drug [placebo or rhTSH-M] in the Core Study). Selected efficacy analyses were also performed on the PPS (comprised of all patients in the FAS who had no major protocol deviations) and All Patients Enrolled in the Extended Follow-up Phase, as indicated. All statistical comparisons were carried out as 2-sided tests. Statistical significance was declared if the p-value was less than or equal to 0.0500, after any pre-planned adjustment for multiple comparison, where applicable.

Primary Endpoint

The analyses of the Core Study primary efficacy endpoint were performed on both the FAS and PPS. The family-wise type I error rate was controlled using the Hochberg procedure. Summary statistics (n, mean, standard deviation [SD], median, minimum, and maximum) of actual, change, and percent

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

change from baseline in goiter volume measured by CT scan were presented by visit and treatment group. Differences between each rhTSH-M dose group and the ^{131}I only group with respect to the percent change from baseline (last measurement prior to treatment) to Month 6 (Visit 8/Early Termination) in goiter volume as measured by CT scan were tested using an analysis of covariance (ANCOVA), with the baseline goiter volume as covariate. Least-square means (LSMs), 95% confidence intervals (CIs) on the differences of LSMs, and p-values on the differences between LSMs were presented. A box plot of percent change from baseline at Month 6 (Visit 8/Early Termination) was also presented by treatment group.

Secondary Endpoints

The analyses of the Core Study secondary efficacy endpoints were performed on the FAS. No adjustment for type I error rate was applied for the secondary efficacy analyses.

Summary statistics (n, mean, SD, median, minimum, and maximum) of the actual, change, and percent change in the SCAT from baseline (SP2) measurements at Month 6 (Visit 8/Early Termination) were presented. Differences between each rhTSH-M dose group and the ^{131}I only group with respect to the percent change from baseline (last measurement prior to treatment) to Month 6 in the SCAT were tested using ANCOVA, with the baseline SCAT as a covariate. Least-square means, 95% CIs on the differences of LSMs, and p-values on the differences between LSMs were also presented. In addition, a box plot of percent changes from baseline at Month 6 (Visit 8/Early Termination) was presented by treatment group.

Frequencies and percentages of ThyQoL goiter-specific items at visits when the ThyQoL was administered (baseline [SP2], Day 5 [Visit 3], Day 90 [Visit 7], and Month 6 [Visit 8/Early Termination]) were presented. Summary of shifts from baseline to Visits 3, 7, and 8 were also presented. In addition, stacked bar charts of percent of patients in each response category versus treatment group by item and by visit were presented.

Actual and change from baseline (SP1) to each post-treatment time point (i.e., Day 2 to Month 6 [Visits 2 to 8/Early Termination, respectively]) in TFTs, including TSH, FT4, TT4, FTI, FT3, and TT3 were summarized descriptively (n, mean, SD, median, minimum, and maximum) by treatment group and visit. The peak values of TSH, FT4, TT4, FT3, and TT3 from baseline up to and including Day 30 ±7 days (Visit 5) were summarized descriptively (n, mean, SD, median, minimum, and maximum) by treatment group. In addition, line graphs of observed levels over time by patient were presented for each treatment group.

The percentage of patients in each treatment group that attained a goiter volume shrinkage of 28% or greater by Month 6 (Visit 8/Early Termination) as measured by CT scan were presented by treatment group. In addition, the baseline goiter volumes of these patients were summarized descriptively (n, mean, SD, median, minimum, and maximum) by treatment group.

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

Tertiary Endpoints

The analyses of the Core Study tertiary efficacy endpoints were performed on the FAS. No adjustment for type I error was applied for the tertiary efficacy analyses.

Goiter volume using ultrasound was calculated as the sum of the volumes of the right and left lobes of the thyroid gland, using the longitudinal, transverse, and horizontal measurements. Actual, change, and percent change from baseline (SP1) to Day 5 and Month 6 (Visits 3 and 8/Early Termination, respectively) in goiter volume as measured by neck ultrasound were summarized descriptively (n, mean, SD, median, minimum, and maximum) by treatment group and visit. Results recorded on the electronic case report form (eCRF) regarding any change from baseline (yes/no; clinically significant/not clinically significant; not assessable) were summarized (number and percent) by treatment group and visit.

Extended Follow-up Phase Secondary Efficacy Endpoints

The analyses of the Extended Follow-up Phase secondary efficacy endpoints were performed on the FAS or All Patients Enrolled in the Extended Follow-up, as indicated. No adjustment for type I error rate was applied for the secondary efficacy analyses.

For goiter volume (measured by CT scan and neck ultrasound) and SCAT (measured by CT scan), actual, change, and percent change in measurements from Baseline (SP2) and Month 6 (Visit 8) to Month 36 (Visit 18) are descriptively summarized by treatment group. For goiter volumes and SCAT as measured by CT, box plots of percent changes from Baseline as well as percent change from Month 6 (Visit 8) at Month 36/Early Term (Visit 18) are presented by treatment group.

Number and percent of patients with or without change from Baseline in goiter volume as assessed by neck ultrasound (Yes/No; CS/NCS; not assessable) are presented by treatment group and visit.

Number and percent of patients in each response category for ThyQoL goiter-specific items at Visits 10, 14, and 18 are presented by visit and treatment group. Summary of shifts in patient response categories for ThyQoL goiter-specific items from Baseline to Month 12, 24, and 36 (Visits 10, 14, and 18, respectively) by visit and treatment group are presented. Summary of shifts from Month 6(Visit 8) to Month 12, 24, and 36 are also presented by visit and treatment group.

Actual and change in TFTs from Baseline (SP1) and Month 6 (Visit 8) to each follow-up visit are descriptively summarized (n, mean, SD, median, minimum, and maximum) by treatment group and visit. For TFT parameters, line graphs of observed levels over time by patient are presented for each treatment group.

SAFETY:

Analyses of AEs and all other safety variables, such as concomitant medications and laboratory assessments, were performed on the Safety Set (comprised of all patients who received 1 dose of the study drug [placebo or rhTSH-M] in the Core Study). Patients were considered, for the safety analyses, to be in

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

the treatment group of the treatment they actually received.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.1, and were summarized by System Organ Class (SOC), Preferred Term, treatment group, and total. All AEs that occurred on or after a patient signed the ICF and before the patient received treatment were categorized as pre-treatment adverse events (PTAEs). All AEs that occurred on or after the initial study treatment (on or after the day of receiving rhTSH-M or placebo) were categorized as treatment-emergent adverse events (TEAEs). The severity, relationship to study drug, action taken, and outcome of the AE were recorded, as well as whether the event was classified as an SAE. The incidence of PTAEs, TEAEs, discontinuations due to AEs, drug-related AEs, severe AEs, and SAEs (including deaths) were summarized. Detailed listings of PTAEs, TEAEs, SAEs, deaths, and discontinuations due to AEs were provided. Inferential comparisons of AE data were not planned.

Summaries or listings of clinical laboratory parameters, serial TFTs, antibodies against rhTSH-M, TSHR-Ab; physical examinations; tracheal diameter measurements; acute, transient change in goiter volume (from baseline to Day 5, measured by ultrasound); ECG findings; respiratory symptoms (directed question); vital signs; and treatment-emergent hyperthyroidism were also provided, as appropriate. Continuous measurements collected at specific time points, as well as the respective changes from baseline, were descriptively summarized. Shifts from baseline were also summarized for the clinical laboratory parameters and physical examinations.

A summary table presents the number and percent of patients who became hypothyroid during the Extended Follow-Up Phase. A hypothyroidism event was recorded as an AE when a principal investigator determined that a patient had become hypothyroid, regardless of TFT results or whether subsequent thyroid supplements were needed.

Additional (Unplanned) Exploratory Analyses

Goiter Shrinkage: A number of exploratory analyses were conducted to investigate any association between goiter shrinkage (by CT scan) and a variety of factors which have been associated with the effectiveness of ^{131}I treatment (baseline 24 hour ^{131}I uptake; therapeutic activity of ^{131}I given; baseline serum TSH value; Visit 2 serum TSH value). Additional analyses were performed to investigate the association between percent change in goiter volume at Month 6 as measured by CT scan with baseline goiter volume measured either by CT scan, or by ultrasound; and, furthermore, the association between baseline goiter volume measured by ultrasound and Month 6 goiter volume measured by ultrasound. The correlation between baseline goiter volume measured by CT scan and baseline goiter volume measured by ultrasound was also explored.

A post-hoc analysis of the differences between each rhTSH-M dose group and the ^{131}I only group with respect to the percent change from baseline (last measurement prior to treatment) to Month 36 in the Core Study primary efficacy parameter (goiter volume as measured by CT scan) were tested using the same

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

method of analysis as the primary endpoint using the FAS. Least-square means (LSMs), 95% CIs on the differences of LSMs, and p-values on the differences between LSMs were therefore presented with the exception that the Hocberg procedure for multiplicity was not applied. Similar analyses for SCAT as measured by CT Scan were also conducted.

Thyroid Function tests: Thyroid status (hyperthyroidism, subclinical hyperthyroidism, disequilibrium, euthyroid, subclinical hypothyroidism, hypothyroidism) were assigned to each patient at a given visit. Thyroid status was assigned based on laboratory TFT data:

- Euthyroid: TSH, TT3, TT4 and FT4 within normal range
- Subclinical Hyperthyroidism: TSH <0.3 uIU/mL; TT3, TT4 and FT4 within normal range
- Hyperthyroidism: TSH <0.3 uIU/mL; TT3 >149 ng/dL or TT4 >12.5 µg/dL or FT4 >1.9 ng/dL
- Subclinical Hypothyroidism: TSH >5.6 uIU/mL but ≤10 uIU/mL; TT3 within normal range or <79.0 ng/dL; TT4 within normal range or <4.5 µg/dL; and FT4 within normal range or <0.7 ng/dL
- Hypothyroidism: TSH >10 uIU/mL, TT3 within normal range or <79.0 ng/dL; TT4 within normal range or <4.5 µg/dL; and FT4 within normal range or <0.7 ng/dL
- Disequilibrium State: Patients who did not fulfil the criteria for any other thyroid status category

This information was used to produce a stacked bar chart which presented the proportion of patients in the 6 defined thyroid states over time during the Core Study in each treatment group, in order to compare post-treatment changes in thyroid status among the 3 treatment groups.

ThyQoL: The SAP specified that frequencies and percents of ThyQoL goiter-specific items, and shifts from baseline, would be presented. As the questionnaire was under development during the study, a number of additional analyses were performed that were not previously planned. An additional summary table was produced to present for each goiter-specific item the number and percentage of patients in one of 4 categories based on their responses at baseline and Month 6: 1) improved; 2) responded 'Not at All' at both baseline and Month 6; 3) no change in response (symptomatic at baseline); and 4) worsened. This analysis was not conducted for the Extended Follow-up Phase.

A composite score was also calculated based on the following 8 question items:

- Sensation of a lump in the throat
- Pressure in the throat
- Need to clear throat frequently

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

- Difficulty swallowing
- Sense of fullness in the neck
- Visible swelling in the front of the neck
- Sensation of suffocating
- Been hoarse

Out of the 12 questions that pertain to physical symptoms of goiter, the 8 questions above were suggested by the ThyQoL instrument developer (external to Genzyme and independent to the study conduct and analyses) for further analysis. These 8 questions are the most likely to be included in the final abbreviated version of the questionnaire to be used in future studies. Summary tables of the composite score comparing the baseline, Month 6, and change from baseline at Month 6, and baseline, Month 36 and change from baseline at Month 36 were produced.

Patients who were Responders: A Mantel Extension Chi-squared test was performed to test the difference in the number of patients between treatment groups achieving the responder rate during the Core Study ($\geq$ 28% goiter volume shrinkage at 6 months).

Safety: The protocol did not stipulate any criteria for investigator reporting of hyperthyroidism or hypothyroidism based on laboratory TFT results as adverse events. Two additional tables were produced to summarize the number and percent of patients with either hyperthyroidism or hypothyroidism up to Day 30 (Visit 1 to 5), and Day 60 to Day 180/end of Core study (Visit 6 to 8) based on laboratory TFT data, to understand any relationship between laboratory values and AE reports. An additional listing of medications used by patients with hyperthyroidism or hypothyroidism (based on laboratory data) during the Core Study was produced.

SUMMARY – CONCLUSIONS

Patient Disposition: A total of 96 patients were randomised: 32 patients to placebo; 31 patients to 0.01mg rhTSH-M and 33 patients to 0.03mg rhTSH-M. Patient [redacted] randomised to the 0.01mg rhTSH-M treatment group did not receive tracer or therapeutic ^{131}I as the Investigator decided to exclude this patient due to aortic valve stenosis deterioration; this patient did not receive study drug. In total, 95 patients received tracer ^{131}I, their randomised study drug treatment and therapeutic ^{131}I. All of these patients completed the Core Study. Four patients declined participation in the Extended Follow-up Phase; therefore 91 patients entered the Extended Follow-up Phase. A total of 6 patients withdrew from the Extended Follow-up Phase: 3 patients in the placebo group, 1 in the 0.01 rhTSH-M group, and 2 in the 0.03 rhTSH-M group. Thus, 85 patients completed the study.

Baseline Characteristics: In the FAS, the 3 treatment groups were similar to each other with respect to most demographics and baseline characteristics. The mean baseline age of all patients was 57.2 years

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

which was similar across treatment groups. The majority of the patients (>75% of each treatment group) in each group were female and Caucasian. The demographics of the patients enrolled in the Extended Follow-up Phase were similar. Medical history was reflective of a reasonably healthy middle-aged population that had goiter and was predominantly female. The majority of patients (85/95, 89%) had normal ECGs at baseline with any abnormalities consistent with the cardiovascular conditions allowed by the study inclusion criteria.

Radioiodine Uptake: Mean tracer ^{131}I activity given was similar among treatment groups. Mean percentage tracer ^{131}I uptake was similar among treatment groups at 24 hours (29% to 31%) and across treatment groups at the 24, 48 and 120-160 hour time points.

Therapeutic Radioiodine Administered: The calculated mean and median activity of therapeutic ^{131}I to be administered were similar in the 0.03g rhTSH-M and placebo groups but lower in the 0.01 mg rhTSH-M group. This was consistent with the lower median baseline goiter size in the 0.01 mg rhTSH-M group. The mean total therapeutic ^{131}I administered was similar among treatment groups, and comparable to mean calculated activity to be given in each group.

Prior and Concomitant Medications: Few patients (15%) took concomitant medications in the 30 days prior to screening.

During the Core Study, thyroid hormones were given for AEs of hypothyroidism in patients receiving placebo (n=2, 6%) or 0.01 mg rhTSH-M (n=1, 3%) patients; and for AEs of hypothyroidism (n=6, 18%) or myxoedema (n=2, 7%) in patients receiving 0.03 mg rhTSH-M. These 11 patients all received levothyroxine sodium as their thyroid hormone with similar doses (often adjusted over time) used across treatment groups (50 to 112 µg [placebo]; 50 µg [0.01 mg rhTSH-M], and 12.5 to 112.5 µg [0.03 mg rhTSH-M]).

During the Extended Follow-up Phase, thyroid hormones were given for subclinical hypothyroidism or hypothyroidism in patients receiving placebo (n=4 [13%]); for hypothyroidism, relative hypothyroidism, subclinical hypothyroidism, thyroiditis, thyrotoxicosis, myxoedema, and growth right thyroid lobe in patients receiving 0.01 mg rhTSH-M (n=9 [31%]); and for subclinical hypothyroidism, hypothyroidism, hypothyroid state, myxoedema, and hypothyroidism prevention in patients receiving 0.03 mg (n=15 [47%]). These 28 patients all received levothyroxine sodium as their thyroid hormone with similar doses (often adjusted over time) used across treatment groups (25 to 175 µg [placebo]; 37.5 to 171 µg [0.01 mg rhTSH-M], and 12.5 to 150 µg [0.03 mg rhTSH-M]).

Of note, although the term “myxoedema” was coded in several patients, no patient in this study developed severe clinical hypothyroidism (as that term might imply in some countries).

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

EFFICACY:

Goiter Volume by CT

The mean and range of baseline goiter volumes were similar among the treatment groups; however, the median goiter size of the 0.01 mg rhTSH-M group (79 mL) was lower than that observed in the placebo (99 mL) and 0.03 mg rhTSH-M (99 mL) groups. An exploratory analysis showed that there was no relationship between initial goiter volume by CT scan and percent reduction in goiter size by CT scan at Month 6.

At Month 6, all treatment groups had a reduction in mean goiter volume by CT scan for the FAS. There was a larger mean percent goiter reduction in the 0.03 mg rhTSH-M group (-33%) compared to 0.01 mg rhTSH-M and placebo (-23% each). The difference in mean percent goiter volume reduction between 0.03 mg rhTSH-M and placebo was statistically significant as tested using analysis of covariance (ANCOVA) and applying the Hochberg procedure, with the baseline goiter volume as the covariate (p=0.0330). The results for the PPS were similar to that of the FAS.

A number of exploratory analyses were conducted to investigate any association between goiter shrinkage (by CT scan) at Month 6 and 1) baseline goiter volume 2) baseline 24 hour ^{131}I uptake, 3) therapeutic activity of ^{131}I given, 4) baseline serum TSH value, 5) Visit 2 serum TSH value and 6) initial screening goiter volume by ultrasound. There was no apparent relationship between goiter shrinkage and any of the aforementioned tested parameters.

At Month 36, All treatment groups also had a reduction in mean goiter volume from baseline. The mean percent goiter reduction from baseline to Month 36 was -44% in the placebo group, -41% in the 0.01 mg rhTSH-M group, and -53% in the 0.03 mg rhTSH-M group. Although not planned in the original analysis plan, a post-hoc analysis demonstrated that there were no statistically significant differences in mean percent goiter volume reduction from baseline to Month 36 between the treatment groups.

Change in SCAT

In the FAS, mean baseline SCAT was similar across treatment groups, though median SCAT was larger in the 0.01 mg rhTSH-M group, a finding in accordance with the lower median baseline goiter volume in this treatment group.

At Month 6, all treatment groups had an increase in mean SCAT compared to baseline. The percentage change from baseline was greatest in the 0.03mg rhTSH-M group (10%) and twice that observed in the placebo (5%) group (and also the 0.01 mg rhTSH-M (4%) group). Neither of the differences between 0.03 mg rhTSH-M and placebo, and 0.01 mg rhTSH-M and placebo, were statistically significant (p=0.1937 and p=0.6355, respectively).

At Month 36, all treatment groups also had an increase in mean SCAT from baseline. The mean percent SCAT increase from baseline to Month 36 was 9% in the placebo group, 4% in the 0.01 mg rhTSH-M

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

group, and 13% in the 0.03 mg rhTSH-M group. Although not planned in the original analysis plan, a post-hoc analysis demonstrated that there were no statistically significant differences in mean percent SCAT increase from baseline to Month 36 between the treatment groups.

ThyQoL

For the 17 goiter-specific items and overall QoL item, many patients did not have symptoms pertaining to several of these questions at baseline. More than 50% of patients reported no baseline symptoms for 9 of these 17 questions. If a particular patient did not have a specific symptom, no improvement in the scoring for this item was possible. Considering only patients that did report symptoms at baseline, the majority of these symptomatic patients reported an improvement in symptoms after treatment for almost all goiter-specific items and in all treatment groups. There was no apparent difference in symptom improvement in the 17 goiter-specific questions and overall QoL question among the treatment groups.

Of the 17 goiter specific questions, 8 questions asked about physical symptoms rather than psychological symptoms. Further analysis of the 8 physical goiter specific questions was performed using a composite score methodology in which a score was assigned for each response (0 for 'Not at all'; 1 for 'A little'; 2 for 'Some'; 3 for 'Quite a bit'; 4 for 'Very much'), totalled and converted for presentation on a scale of 0 to 100.

At baseline, the summary statistics for baseline composite score were not similar across treatment groups; mean, median and the upper limit of the score range were all lowest in the 0.03 mg rhTSH-M group (21.4, 18.8 and 50 respectively) compared to placebo (24.5, 18.8 and 81 respectively) and 0.01 mg rhTSH-M groups (29.0, 28.1 and 69 respectively).

At Month 6, the change from baseline was an approximately 50% reduction (i.e., symptom improvement) in the mean and median composite score in all treatment groups. The mean change from baseline composite score was -9.7, -18.2 and -11.1 for the placebo, 0.01 mg rhTSH-M and 0.03 mg rhTSH-M groups respectively. The median change from baseline composite score being -12.5 across all treatment groups. The 95% confidence intervals of the mean changes in composite score indicated that these are significant improvements.

At Month 36, the mean change from baseline composite score was -16.6, -17.1, and -11.5 for the placebo, 0.01 mg rhTSH-M, and 0.03 mg rhTSH-M groups, respectively. The 95% confidence intervals of the mean changes in composite score at Month 36 indicated that the patients continued to experience significant improvements.

The absence of a notable effect with rhTSH-M treatment compared to placebo for symptom improvement in goiter specific items and also composite score change could be the result from 1) the study not being powered to detect a true difference, 2) relatively asymptomatic patients were present in the study, 3) more symptomatic patients (according to the ThyQoL) were not evenly distributed across treatment groups at

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

baseline or 4) the questionnaire was not sensitive enough to detect true differences.

At Month 6, the mean VAS score at baseline was similar among placebo, 0.01 mg rhTSH-M and 0.03 mg rhTSH-M groups (73.0, 72.8, 76.3 respectively), with no discernible change in the mean VAS scores across treatment groups (74.3, 75.9, 74.7 respectively). VAS was not evaluated at Month 36.

Changes in Thyroid Function Tests

TSH: TSH values rapidly peaked at Day 2 in the rhTSH-M groups, most noticeably in the 0.03 mg rhTSH-M group. Mean TSH values did not exceed the normal range, though some individual patient values did. At Days 5 to 30, mean TSH values were below baseline values; mean TSH values were higher than baseline at Days 60 to Month 36. No change in TSH values was observed in the placebo group at Day 2, (the day after the placebo injection).

Total T3: Mean Total T3 values were highest at Day 14 in the placebo and 0.01 mg rhTSH-M groups, but highest at Day 30 in the 0.03 mg rhTSH-M group. Mean Total T3 was elevated for a longer period of time in the 0.03 mg group compared to other groups; this may have resulted from prolonged release of thyroid hormones from damaged goiter tissue. At Day 60 to Month 36, mean T3 values were similar to baseline.

Free T3: Mean Free T3 values were also highest at Day 14 in the placebo and 0.01 mg rhTSH-M groups, but highest at Day 30 in the 0.03 mg rhTSH-M group. At Day 60 to Month 36, mean Free T3 values were slightly lower or equal to baseline.

Total T4: Mean total T4 values were highest at Day 14 in the placebo and 0.01 mg rhTSH-M groups, but highest at Day 5 in the 0.03 mg rhTSH-M group. At Day 60 to Month 12, mean Total T4 values were slightly lower than baseline for all groups. Mean total T4 values increased from Month 15 to Month 36.

Free T4: Mean free T4 were highest at Day 14 in the placebo and 0.01 mg rhTSH-M groups, but highest at Day 30 in the 0.03 mg rhTSH-M group. At Day 60 to Month 36, mean Free T4 values were slightly lower than baseline values.

Though mean values of thyroid hormones in the 0.03 mg rhTSH-M group were highest at different times than in the 0.01mg rhTSH-M and placebo groups, mean values for all thyroid hormones were elevated over a prolonged period with little difference in mean thyroid hormone values over Day 5 to Day 30 in the 0.03 mg rhTSH-M group.

Patients were assigned a thyroid status at each visit to comprehend the changes in TFT. At baseline, the majority of patients were euthyroid at study entry (Placebo 67%, 0.01 mg rhTSH-M 53%, 0.03 mg rhTSH-M 61%), though approximately one-third of patients in all treatment groups were subclinically hyperthyroid at baseline (Placebo 31%, 0.01 mg rhTSH-M 40%, 0.03 mg rhTSH-M 39%). At Day 5 and 14 (Visits 3 and 4), where mean serum TSH levels dropped below the lower limit of the normal range (0.3 to 5.6 uIU/mL) due to rising levels of thyroid hormones released from damaged goiter tissue; an

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

increasing proportion of patients became subclinically hyperthyroid or hyperthyroid in all treatment groups. The highest proportion of patients who were subclinically hyperthyroid (Placebo 63%, 0.01 mg rhTSH-M 57%, 0.03 mg rhTSH-M 44%) or hyperthyroid (Placebo 28%, 0.01 mg rhTSH-M 33%, 0.03 mg rhTSH-M 47%) occurred at Day 14 in all treatment groups.

At Day 30, the thyroid status profile began to change, with a decline in the proportion of subclinically hyperthyroid (Placebo 59%, 0.01 mg rhTSH-M 53%, 0.03 mg rhTSH-M 45%), and hyperthyroid patients (Placebo 16%, 0.01 mg rhTSH-M 30%, 0.03 mg rhTSH-M 40%) in all treatment groups as patients began to progress back to euthyroidism. At Day 60 (Visit 6) the percentages of patients in the placebo, 0.01 mg rhTSH-M and 0.03 mg rhTSH-M groups who were subclinically hyperthyroid were 16%, 38% and 36%, respectively; the percentages of patients who had hyperthyroidism were 3%, 3% and 12%, respectively; while the percentages of euthyroid patients were 63%, 52% and 27% respectively. At Visit 8, 75% of placebo patients, 60% of 0.01 mg rhTSH-M and 52% of 0.03 mg rhTSH-M patients were euthyroid.

At Day 60, Day 90 and Day 180, more patients were hypothyroid or subclinically hypothyroid in the 0.03 mg rhTSH-M group (12% and 18% respectively) compared to 0.01 mg rhTSH-M (20% and 0%, respectively) and placebo (3% and 0% respectively). This is a likely consequence of loss of thyroid function due to the overall greater mean goiter shrinkage seen in this group. It is expected that these hypothyroid patients will become biochemically euthyroid by taking chronic thyroxine therapy to maintain euthyroid status.

To conclude, there was progression after study treatment of most patients to subclinical hyperthyroidism or hyperthyroidism and back to the euthyroid state over the 6 month period of the Core Study.

<u>Percentage of Patients who were Responders</u>

A clinically significant response (responder rate) was pre-defined as ≥ 28% reduction in goiter size at Month 6, based on a review of published literature at the time. At Month 6, the 0.03 mg rhTSH-M group had the highest proportion of responders (64% [21/33 patients]), followed by the 0.01 mg rhTSH-M group (37% [11/30 patients]) and then the placebo group (25% [8/32 patients]). The difference in the greater proportion of responders in the 0.03 mg rhTSH-M group compared to placebo was statistically significant ($p=0.0017$ using the Mantel Extension Chi-squared test).

Amongst patients achieving responder status, the greatest mean percent reduction in goiter volume at Month 6 was in the 0.03 mg rhTSH-M group (-45%) compared to 0.01mg rhTSH-M (-40%) and placebo (-35%) groups. The overall mean, median and range of baseline goiter sizes among responder patients in the treatment groups were similar.

A responder analysis was not conducted for the Extended Follow-up Phase.

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

Goiter Volume as Measured by Ultrasound

Baseline goiter values were similar across treatment groups in the FAS as measured by ultrasound, though the values were approximately 20-30% lower than those measured by CT scan.

At Month 6, all treatment groups had a reduction in mean goiter volume as measured by ultrasound, though the largest percent mean reduction in goiter size was in the 0.01 mg rhTSH-M group (-37%) compared to placebo (-29%) and 0.03mg rhTSH-M (-26%). This contrasted with the results of percent mean reduction in goiter volume by CT scan for the primary endpoint in which the 0.03 mg rhTSH-M group had the greatest mean percent reduction in goiter volume.

At Month 36, all treatments groups had a reduction in mean goiter volume as measured by ultrasound. The mean percent goiter reduction as measured by ultrasound from baseline to Month 36 was -49% in the placebo group, -51% in the 0.01 mg rhTSH-M group, and -53% in the 0.03 mg rhTSH-M group.

SAFETY:

Adverse Events

Throughout the 36 month study duration, a total of 410 TEAEs were reported in 84 (88%) of the 95 patients in the Safety Set. In general, AEs coded to similar SOCs among the 3 treatment groups. The highest frequency of AEs occurred in the MedDRA SOC of Endocrine Disorders with 67 events occurring in 45 (47%) patients. More patients in both the rhTSH-M groups reported AEs of Hyperthyroidism (9 events in 8/30 patients [27%, 0.01 mg rhTSH-M]; 12 events in 11/33 patients [33%, 0.03 mg rhTSH-M]) compared to placebo (2 events in 2/32 patients [6%]). More patients in both the rhTSH-M groups reported AEs of Hypothyroidism (10 events in 10/30 patients [33%, 0.01 mg rhTSH-M]; 15 events in 15/33 patients [45%, 0.03 mg rhTSH-M]) compared to the placebo group (5 events in 4/32 patients [13%]). In the Musculoskeletal and Connective Tissue Disorders SOC, the PT of neck pain was the most frequently reported event in this SOC (6/33 [18%] patients in the 0.03mg rhTSH-M group, 3/30 [10%] patients in the 0.01 mg rhTSH-M group, and 3/32 [9%] patients in the placebo group). The other most frequently (>5% patients) occurring treatment emergent AEs across all SOCs (by MedDRA Preferred Term) were headache (12 events in 11 [12%] patients), hypertension (10 events in 9 [9%] patients), cough (8 events in 7 [7%] patients), goitre (8 events in 6 [6%] patients), sinusitis (7 events in 5 [5%] patients), urinary tract infection (6 events in 5 [5%] patients), abdominal pain (5 events in 5 [5%] patients), nausea (5 events in 5 [5%] patients), and back pain (5 events in 5 [5%] patients).

The majority of AEs were of mild (302/410 events) or moderate severity (97/410 events). Only 7 patients (11 events in 7 [7%]) patients) reported severe AEs which occurred in 4 placebo patients (1 event of vitreous floaters in 1 patient, 1 event of neck pain in 1 patient, 1 event of cholelithiasis in 1 patient, and 1 event each of cellulitis, staphylococcal bacteraemia and amputation revision in 1 patient), one 0.01 rhTSH-M patient (1 event of wrist fracture in 1 patient), and two 0.03 mg rhTSH-M treatment

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

patients (1 event each of back pain and pain in extremity in 1 patient and 1 event each of neck pain and hypertension in 1 patient). Only the event of neck pain was considered by the investigator to be related to study drug (0.03 mg rhTSH-M), while all other severe AE events were considered not related to study drug.

In the Safety Set, a total of 92 events in 47 patients (47/95, 49%) regardless of severity, were considered by the investigator as related to study drug treatment. All but 1 treatment-related AEs were of mild or moderate severity; 1 event of neck pain in 1 patient in the 0.03 rhTSH-M group was considered by the investigator as definitely related. More AEs were considered related to rhTSH-M treatment groups than placebo. The highest frequency of related AEs in all treatment groups occurred in the MedDRA SOC of Endocrine Disorders (34 [36%] patients). The most frequently occurring related AEs across all treatment groups were (by MedDRA PT) hypothyroidism (21 [22%] patients), hyperthyroidism (16 [17%] patients), and neck pain (12 [13%] patients. Otherwise, most related TEAE were reported by one isolated patient in a treatment group within a SOC.

SAEs

Throughout the 36 month study duration, 26 SAEs were reported in 16 (17%) patients for the Safety Set. Three SAEs occurred during the Core Study; the remainder occurred during the Extended Follow-up Phase. In general, SAEs coded to similar SOCs among the treatment groups. The majority of treatment emergent SAEs occurred in a single patient each. SAEs occurring in more than 1 patient included (by MedDRA preferred term): atrial fibrillation (2 events in 2 [7%] patients in the 0.01 mg rhTSH-M group), myocardial infarction (2 events in 2 [6%] patients in the 0.03 mg rhTSH-M group), and cellulitis (1 event in 1 [3%] patient in the placebo group and 1 event in 1 [3%] patient in the 0.03 mg rhTSH-M group). Please see Section 14.3.3 for complete narratives for these events.

Deaths

No patients died during the study.

Discontinuations Due to Adverse Events

No patients withdrew from the study due to an AE.

Hyperthyroidism

Based on laboratory TFT, most patients became either subclinically hyperthyroid and/or hyperthyroid (Placebo 29/32 patients, 0.01 mg rhTSH-M 28/30 patients, 0.03 mg rhTSH-M 32/33 patients) during the first 30 days of the Core Study. This was not unexpected considering that thyroid hormones were released from damaged goiter tissue. Only 1 patient received medication for the indication of hyperthyroidism based on TFT alone. Compared to laboratory TFT results obtained in this time frame, (which were used to define whether patients were subclinically hyperthyroid or hyperthyroid), relatively few patients in the study (21/95) reported AEs of hyperthyroidism and the majority of patients (15/21) did

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

not receive any medications for AEs of hyperthyroidism. During the Core Study, more AEs of hyperthyroidism were reported in patients receiving 0.03 mg rhTSH-M (11/32 patient 33%) compared to 0.01 mg rhTSH-M (8/30, 27%) and placebo (2/32, 6%). There were no specific guidelines for investigators within the rhTSH-M01505 protocol regarding reporting of AEs of hyperthyroidism based on laboratory values, though general AE reporting criteria suggest reporting laboratory abnormalities that are of clinical significance and/or require an alteration of medical care as AE, applied. Patient [redacted] was treated briefly for hyperthyroidism in the Core Study and was diagnosed with Graves' disease (i.e., Basedow's disease) 9 months after study drug treatment for which she received medication. No other AEs of hyperthyroidism or thyrotoxicosis were reported during the Extended Follow-up Phase.

<u>Hypothyroidism</u>

Based on laboratory TFT, some patients became either subclinically hypothyroid and/or hypothyroid during the latter part of the Core Study (Days 60 to 180). More patients in the rhTSH-M treatment groups (0.01 mg rhTSH-M 7/30 patients, 0.03 mg rhTSH-M 12/33 patients) were hypothyroid based on TFTs during Days 60 to180 than the placebo group (3/32 patients). Overall 29 patients (17 during Core Study) in the study experienced an AE of hypothyroidism. Laboratory definitions of hypothyroidism were generally consistent with the AEs of hypothyroidism reported in the majority of patients (15/20 patients). More AEs of hypothyroidism were reported in patients receiving 0.03 mg rhTSH-M (15/33) compared to 0.01 mg rhTSH-M (10/30) and placebo (4/32). Eleven patients (Placebo =2, 0.01 mg rhTSH-M =1, 0.03 mg rhTSH-M =8) received thyroid hormone supplementation for hypothyroidism, of which the majority (8/11) were on thyroid hormones at the end of the core study (Month 6).

During the Extended Follow-up Phase, 12 patients experienced an AE of hypothyroidism (2/30 patients in the placebo group, 5/29 patients in the 0.01 mg rhTSH-M group, and 5/32 patients in the 0.03 mg rhTSH-M group). At 36 months, the number of patients on chronic thyroid hormone replacement in the placebo, 0.01 mg rhTSH-M, and 0.03 mg rhTSH-M groups were 4 (13%), 9 (31%), and 15 (47%), respectively.

<u>Transient Goiter Swelling</u>

At Day 5, the mean goiter volume in the 0.03 mg rhTSH-M group increased by 9.5% compared to baseline (SP1). This contrasts with a small reduction (approximately 4%) in mean goiter volume at Day 5 in the placebo and 0.01 mg rhTSH-M groups. This did not correlate with reports of goiter tenderness as part of the physical exam at Day 7 which was similarly reported across groups at this time point.

There was only 1 AE of Local swelling (of the neck) reported by a patient receiving 0.03 mg rhTSH-M. Analysis of potentially related events of Neck pain, Thyroid pain and Goiter did not correlate with any changes in goiter size as measured by ultrasound. The significance of any transient goiter swelling by ultrasound is unclear considering this is a relatively inaccurate technology compared to CT scan.

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

Laboratory Values

There were no meaningful changes in hematology or serum chemistry parameters.

Vital Signs and Physical Examination

No clinically meaningful changes or shifts in the complete physical exam were observed. Very few patients (≤3) in any treatment group reported any new cardiac symptoms as part of the abbreviated physical exam at days, 7, 14, and 30. More patients in the 0.03 mg rhTSH-M group (11/33 patients) reported some goiter tenderness at Day 14 compared to 0.01 mg rhTSH-M (7/30) and placebo groups (8/32) as part of the abbreviated physical exam.

No clinically meaningful changes in vital signs were observed.

ECG

Though there were post-treatment ECG findings, the majority of these were not considered clinically significant. Any clinically significant findings were reported as AE under the Cardiac Disorders SOC. Of note, only one ECG was performed per patient at each visit and any abnormalities were not identified from duplicated measurements.

The mean and median baseline ECG measurements for each treatment group were comparable across treatment groups. There were no notable changes in the mean or median ECG measurements in any treatment group at any visit post study drug treatment.

Two patients with brief atrial fibrillation were mentioned previously in the SAE section.

Six patients (n=3, 0.01 mg rhTSH-M; n=3 placebo) had a change (increase) from baseline QT interval of ≥0.06 seconds (60 milliseconds). In five of these patients, the QT interval remained within the normal range (0.30 to 0.45 seconds). Only one of these six patients demonstrated QT prolongation above the upper limit of the normal range (>450 milliseconds). This patient had a QT interval of 0.51 seconds (Visit 5), with an increase of 0.12 seconds from baseline (0.39 seconds) which was reported as an AE of Electrocardiogram QT prolonged. This patient was in the 0.01 mg rhTSH-M group. The event began 5 days after receiving rhTSH-M, was considered mild in severity, no action was taken, and the event resolved 9 days later.

ECGs were not assessed during the Extended Follow-up Phase.

Other Safety Measures

rhTSH-M antibodies

There was no evidence of formation of antibodies against rhTSH-M.

TSHR-Ab

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
+1 (617) 252-7500

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
+31 35 699 1200

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** recombinant human TSH-modified **NAME OF ACTIVE INGREDIENT** Thyrotropin alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

As the Core Study was finishing, the Vendor learned that they only had shelf-life quality data for these samples for 3 months. In light of this finding, the samples were run anyway for information though any results must be interpreted with caution.

Seven patients had TSH receptor antibody scores >15 of which 2 patients reported AE of hyperthyroidism. The clinical significance of changes in TSH receptor antibody scores in relation to potential hyperthyroidism is unclear. In total, 11 patients (n=1 placebo, n=5, 0.01 mg rhTSH-M and n=5, 0.03 mg rhTSH-M) had samples taken at Visit 6 and/or Visit 7 as a result of having hyperthyroidism, and all 11 patients reported an AE of hyperthyroidism. In 10 patients, hyperthyroidism was considered clinically significant. None of these patients had a TSH Receptor antibody value >15. Twenty patients across treatment groups reported an AE of hyperthyroidism during the study, but only 3 of these patients were found to have had an important change in TSH Receptor antibody value.

Respiratory Directed Question

No clinically meaningful changes in the distribution of the Respiratory Directed Question were observed.

HSS Score

No clinically meaningful changes in the distribution of HSS scores were observed. No (0%) patient had a HSS score ≥20 during the core study and so no AE of "hyperthyroidism (HSS)" were reported.

CONCLUSION:

[redacted]