SYNOPSIS

NAME OF COMPANY **Genzyme Corporation** 500 Kendall Street Cambridge, MA 02142, USA **Genzyme Europe BV** Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** Thyrogen® **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:

Follow-up of Thyroid Cancer Patients from Study THYR-008-00 Who Received Thyroid Remnant Ablation Using Either the Hypothyroid or the Thyrogen Method

Investigators: [redacted]

Study Centers: [redacted]

Publication (reference):

Not applicable.

Study Period:

The first patient was enrolled on 03 May 2006. The last patient completed the final study visit on 21 July 2006.

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Objectives:

Primary objective:

To confirm the status of thyroid remnant ablation by using Thyrogen-stimulated radioiodine static neck imaging in patients previously treated in the THYR-008-00 study.

Secondary objectives:

To learn if there was recurrence of thyroid cancer in any of the patients previously treated in the THYR-008-00 study.

To assess Thyrogen-stimulated serum thyroglobulin (Tg) measurements in patients previously treated in the THYR-008-00 study.

To assess safety information on repeat exposure to Thyrogen in patients previously treated in the THYR-008-00 study.

Methodology:

Patients who had previously completed THYR-008-00 were asked to give consent for review of their medical records to capture medical information between when they were last seen for that study and the present. The patients were also asked to undergo some prospective medical tests.

In THYR-008-00, patients were randomized to be prepared for post-thyroidectomy thyroid remnant ablation with either standard hypothyroidism or use of Thyrogen while euthyroid. All patients received 100 millicuries (mCi) (3.7 Gigabecquerels [GBq]) ^{131}-radioiodine (^{131}I) to ablate thyroid remnants and had follow-up diagnostic whole body scan (WBS) and static neck imaging performed approximately 8 months later. The last patient completed the final study visit on 26 September 2003.

In this Phase 3 follow-up study, to provide information on their current status, patients were asked to undergo Thyrogen-stimulated diagnostic whole-body scanning and static neck imaging to assess neck uptake visually and by neck-uptake quantitation. Patients received Thyrogen on 2 consecutive days ("Monday and Tuesday"), then ^{131}I orally (PO) 24 ±6 hours after the second injection of Thyrogen ("Wednesday"), followed 48 ±6 hours after the isotope (4 mCi [148 Megabecquerels (MBq)] of ^{131}I was used) by the WBS and static neck imaging ("Friday"). Neck scans were read in a blinded manner by 3 independent, expert central readers (hereafter referred to as central readers) and the Dosimetry Coordination Centre (DCC). The definition of successful ablation by scanning was no visible thyroid bed uptake, or if visible, then thyroid bed uptake <0.1% of administered isotope.

A basal serum Tg sample was drawn just before the first injection of Thyrogen ("Monday"), and a second serum Tg sample was drawn 72 ± 6 hours after the second injection of Thyrogen ("Friday"). Serum samples were frozen and shipped to a central laboratory. Each serum sample also had the level of anti-Tg antibodies determined. Patients whose samples contained clinically significant levels of anti-Tg

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antibodies were excluded from final analyses of Tg values. The definition of successful ablation by serum Tg assessment was Thyrogen-stimulated serum Tg level <2 ng/mL.

Investigators, patients, and site staff were unblinded to the original treatment assignment in THYR-008-00, but static neck imaging in this follow-up study was read by central readers blinded to the prior treatment identity.

Of note, different criteria for successful ablation could give slightly different response rates. Scan results have been chosen as the primary endpoint. After exclusion of patients with anti-Tg antibodies, success of ablation was also assessed using Thyrogen-stimulated Tg levels as a secondary endpoint.

Serum thyroid-stimulating hormone (TSH), free thyroxine (T4), a pregnancy test in women of child-bearing potential, and a physical exam was conducted at the start of prospective medical testing. It was not necessary to repeat these measures again after the WBS and static neck imaging were completed.

Adverse events (AEs) and concomitant medications were recorded for the period between signing of the informed consent form and completion of protocol-specified procedures at Visit 4.

Number of Patients (planned and analysed):

Up to 61 of the 63 original patients who previously completed the original THYR-008-00 study were planned to be screened and enrolled in this follow-up study. All 61 patients were contacted, but only 51 agreed to participate.

Expected eligible patients for the study: 61

A total of 48 patients were analysed; 27 from the former Euthyroid group and 21 from the former Hypothyroid group. All 48 patients were in the Intent-to-Treat (ITT) and the Per-Protocol (PP) populations.

Patients with only retrospective medical data collected: 3

Patients who declined to participate: 10

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion criteria:

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

1. Committed to follow the protocol requirements, as evidenced by providing written informed consent before any study-related procedures are performed and within 28 days prior to Day 1;
2. Completed the THYR-008-00 study;
3. A negative serum pregnancy test within 8 days prior to the start of the week during which the patient will receive Thyrogen and radioiodine (required for all pre-menopausal women of

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child-bearing potential, with menopause defined as age >50 years with >2 years without a menstrual period).

Exclusion criteria:

Patients with any of the following characteristics were not eligible for inclusion in the study:

1. Patients who are currently taking amiodarone or other prescribed iodine-containing medication;
2. Patients who received iodine-containing X-ray contrast material within the prior 3 months;
3. Women of child-bearing potential, unless confirmed to have a negative pregnancy test prior to dosing;
4. Women who are pregnant or lactating;
5. Patients who are currently participating in another investigational drug study or who have participated in such a study within 30 days of their enrollment in this study;
6. Patients who are unwilling or unable to complete all the required study procedures per protocol (with the exception of patients for whom scanning could pose a medical risk);
7. The patient who by mistake received only one-half the intended dose of Thyrogen during THYR-008-00 (Patient identifier not disclosed);
8. The patient in THYR-008-00 who was found to have lung metastases on her post-therapy scan (Patient identifier not disclosed);
9. 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 an impact on the capability of the patient to adequately comply with the requirements of this study.

Test Product, Dose, and Mode of Administration; Batch Number:

Thyrogen 0.9 mg daily, administered intramuscularly (IM) in the buttock on 2 consecutive days.
For WBS and static neck imaging, each patient received 4 mCi (148 MBq) ± 0.4 mCi ^{131}I PO.

Batch numbers used were [redacted]).

Duration of Treatment:

Patient enrollment was completed in approximately 2.5 months.

The screening period lasted up to 28 days for each patient enrolled in the study, during which medical history data were collected; also, in some patients prospective screening tests were performed. The Treatment Period for each patient lasted 5 days. During the Treatment Period, the primary and secondary endpoint data were collected. For the purposes of data collection and analysis, the study period was defined as the time from the signing of informed consent to up to 10 days following the completion of Visit 4.

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Reference Therapy, Dose and Mode of Administration; Batch Number:

No reference therapy was given. All patients in this follow-up study received Thyrogen as described above.

Criteria for Evaluation:

Efficacy:

Primary Endpoint

Static neck imaging: Treatment success is defined as patients having a negative neck scan (i.e., "no visible uptake or if visible below 0.1% uptake in the thyroid bed"), as determined by eye by the 3 central readers following the diagnostic scan, and by the quantified result by DCC.

Secondary Endpoints

Disease recurrence: An assessment as to whether thyroid cancer had recurred at any time since the completion of THYR-008-00 was completed for each patient by the Investigator.

Serum Tg levels: Successful ablation, as assessed by the serum Tg level, required that the Thyrogen-stimulated Tg level was <2 ng/mL. Results of serum Tg level assays and tests for anti-Tg antibody were provided by the central laboratory and interpreted by the PIs.

Safety:

The general safety and tolerability of Thyrogen were assessed through patient-reported AEs and serious adverse events (SAEs). In addition, safety was also assessed by changes in laboratory assessments, vital signs (including blood pressure, temperature, heart rate, and respiratory rate), and changes in medical history or physical exam findings.

Statistical Methods:

As this was a follow-up study, the sample size consisted of the number of patients who completed the THYR-008-00 study and consented to participate in this follow-up study. Using the standard non-inferiority framework, with at least 25 patients per arm, it was possible to exclude a difference of 20% in the ablation rates. Assuming ablation rates of 93% for both treatment arms, the probability that the 1-sided 97.5% confidence interval (CI) on the difference between the ablation rates in the 2 treatment groups excludes values of 20% or greater was 79%. The standard alpha=0.05 was used to assess statistical significance. Missing or invalid data were not imputed.

Efficacy:

Efficacy analyses were based on the ITT population (which included all patients who completed the THYR-008-00 study, provided consent and enrolled in this study, and were confirmed to be eligible for entry into the study) and the PP population (a subset of the ITT population) for purposes of assessing overall response. The PP population consisted of patients who completed the THYR-008-00 study,

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enrolled in this study, were confirmed to be eligible for entry into this study, and did not have protocol violations or deviations that impacted the efficacy assessments.

Neck scan results were the primary efficacy endpoint in this study. Patients with a negative neck scan (i.e., "no visible uptake or, if visible, below 0.1% uptake in the thyroid bed") as determined by the 3 central readers and by the quantified uptake measurements performed by the DCC at the University of Würzburg, Würzburg, Germany, following the diagnostic scan were considered treatment successes. The proportion of patients demonstrating treatment success following the diagnostic scan was determined for each treatment group in the THYR-008-00 study. The difference in success rates for the 2 arms was reported with a 95% CI.

As a secondary efficacy endpoint, for each patient the Investigator completed an assessment as to whether thyroid cancer had recurred at any time since the completion of the THYR-008-00 study. This assessment was based on a review of all relevant medical data retrieved since the close of the THYR-008-00 study, as well as data collected during the present study. The latter included the Thyrogen-stimulated diagnostic scan and Tg levels (as specified in the THYR01605 protocol), and may have included results of medical procedures (e.g., computed tomography [CT] scans, magnetic resonance imaging [MRI] scans, neck ultrasound exams, positron emission tomography [PET] scans, aspirations, or biopsies) that were collected during the timeframe of the THYR01605 study as part of routine clinical follow-up care. The assessment regarding recurrence was designated as definitive cancer recurrence, possible cancer recurrence, no evidence of cancer recurrence, or "cannot assess" (with the reason specified).

During this assessment, serum samples were identified that contained clinically significant levels of anti-Tg antibodies. Assuming there was no other known source of Tg (such as known metastasis), the definition of successful ablation by serum Tg assessment was a Thyrogen-stimulated serum Tg level <2 ng/mL. The proportion of patients demonstrating treatment success was calculated for each treatment group in the THYR-008-00 study. Ninety-five percent CIs of the difference in the proportion of patients with successful ablation were provided both for the diagnostic scan assessment and the serum Tg assessment. However, patients whose samples contained clinically significant levels of anti-Tg antibodies were excluded from the final analyses of Tg values. Patients who received additional therapeutic radioiodine since the close of the THYR-008-00 study were also excluded from the final analyses of ablation success, but these patients were not excluded from the assessment of cancer recurrence since the close of the prior study. Basal Tg and Thyrogen-stimulated Tg levels were summarized descriptively by treatment group.

Safety:

Safety analyses were performed on the safety population, which included all patients who signed the informed consent. The assessment of safety was a secondary endpoint in this study. Recording of any events began after the informed consent was signed and ended when protocol procedures during Visit 4 were completed.

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AEs were classified using the Medical Dictionary for Regulatory Activities. All AEs were displayed in patient listings. The safety assessment was based on the incidence of treatment-emergent AEs, including summaries of SAEs, AEs leading to withdrawal, and AEs deemed related to study treatment.

AEs were categorized and tabulated by system organ class, preferred term, treatment group in THYR-008-00, intensity, seriousness, and relationship to study treatment. Additionally, discontinuations due to AEs were summarized by treatment group in the preceding study. Information collected during the screening period was presented separately from treatment-emergent signs and symptoms.

Changes from baseline in clinical laboratory tests were also summarized. The analysis of laboratory values was based on frequencies of abnormal values and frequencies of clinically significant abnormal values. Safety data were provided using counts and percentages if data were categorical, and by number of non-missing observations, mean, median, standard deviation and range if data were continuous. Information collected during the screening period was presented separately from treatment-emergent signs and symptoms. Abnormal clinical laboratory values were noted as either high or low based on the normal ranges. Changes from baseline in laboratory parameters were summarized by the treatment group in the previous study. TSH and free T4 levels were summarized descriptively by treatment group.

Summary – Conclusions:

Demographics:

Overall, 51 of the 61 eligible patients (23 in the former Hypothyroid group and 28 in the former Euthyroid group) enrolled in this follow-up study, a median of 3.7 years (range from 3.4 to 4.4 years) since they completed the THYR-008-00 study.

The 51 patients had a mean age of 48.3 years when they consented to participate in this follow-up study, and the population consisted of 41 (80%) females and 10 (20%) males. The demographic parameters (e.g., race, weight, height, and body mass index) were similar between the 2 former treatment groups, and were in similar proportion to all 63 patients who had been enrolled in THYR-008-00. In this follow-up study, 45 patients (88%) had initially been diagnosed with papillary thyroid carcinoma, and 6 (12%) had been diagnosed with papillary and follicular carcinoma, and were similarly distributed between the two former treatment groups.

Most medical or surgical histories were similarly distributed across the 2 former treatment groups. A higher percentage of patients in the former Euthyroid group than in the former Hypothyroid group had an interim medical history for the Musculoskeletal system (11% and 0%, respectively), and the Cardiovascular system (18% and 0%, respectively), which does not appear to be due to factors related to the Investigators.

Also, a higher percentage of patients in the former Euthyroid group than in the former Hypothyroid group had a reported interim medical history in the Metabolic/Endocrine/Nutritional system (36% and

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17%, respectively). In reality, Investigators should have reported a history in this system for all patients. All patients had a medical or surgical history in the Metabolic/Endocrine/Nutritional body system recorded during the THYR-008-00 study.

Efficacy Results:

Primary Endpoint - Static neck imaging:
Forty-three (43) patients received 4 mCi (148 MBq) radioiodine for scanning, and all 43 patients had interpretable scans. The majority of the central readers agreed on the observation of no uptake anywhere on each WBS, except for uptake in the thyroid bed in 5 scans (1 patient in the former Hypothyroid group and 4 patients in the former Euthyroid group). The neck portion of the WBS was the only part that was informative. However, in all 5 of those scans the amount of uptake was far below the *a priori* cut-off of < 0.1%. Thus, the neck scans performed a median of 3.7 years after the ablation performed during the THYR-008-00 study showed 100% of patients in both treatment groups with interpretable scans were still successfully ablated, using the primary endpoint of "no visible uptake or, if visible, <0.1% uptake."

One caveat, however, is that any patients who had received additional therapeutic radioiodine since the end of the THYR-008-00 study could confound the interpretation of the follow-up neck image (i.e., assessment of the original remnant ablation effort). Five patients in the former Hypothyroid group (22%) and 4 patients in the former Euthyroid group (14%) had received therapeutic ^{131}I therapy during the period between the two studies. Excluding the data for these 9 patients, 100% of patients in both treatment groups were still successfully ablated.

Secondary Endpoint - Disease recurrence:
Since the end of the THYR-008-00 study, no patients had a definitive cancer recurrence reported by the study Investigators and 48/51 patients (94%) had no evidence of cancer recurrence. One patient (in the former Euthyroid group) had possible cancer recurrence and 2 patients (1 in each of the former Hypothyroid and Euthyroid groups) could not be assessed.

During the period between the two studies, 6 patients had CT scans, 1 had an MRI scan, 6 had diagnostic radioiodine scans, 38 had neck ultrasound exams, 3 had PET scans, and 5 had node or mass aspirations or biopsies. Also, 9 patients had high-level radioiodine therapy during the interim period (5 patients in the former Hypothyroid group and 4 patients in the former Euthyroid group). In 4 patients this therapy was reported as being given for thyroid tumor treatment, and for 5 patients it was for completion of remnant ablation. In 3 of these 5 cases, the completion of ablation with additional radioiodine occurred in patients who had persistently elevated serum Tg levels, rather than an actual determination by ultrasound, CT or MRI that a thyroid remnant possibly remained in the neck. Post-therapeutic radioiodine WBSs were also done in 8 of these 9 patients.

The mean percent of radioiodine (^{131}I) uptake on the static neck scans at Visit 4 was very low (0.009%) for patients with radioiodine uptake data in both the former Hypothyroid (n=18) and Euthyroid (n=25) groups.

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In addition to the assessments by the 3 central readers, the WBS/static neck imaging results were locally interpreted by the Investigator, who identified 40 patients as being negative and 3 patients as being positive with trace uptake in the thyroid bed. The Investigator's findings did not completely agree with the patients identified by the central readers, which illustrates that this is a relatively equivocal finding. Trace uptake in the thyroid bed is believed to have no long term pathological significance.

Secondary Endpoint - Serum Tg levels:
Tg is a sensitive but nonspecific indicator of the possible presence of normal thyroid remnant tissue, which could come either from thyroid remnant tissue or from small amounts of residual tumor present in neck lymph nodes or other locations. This is especially true in this group of 51 cancer patients, 19 of whom had neck node involvement at the beginning of the THYR-008-00 study. A patient might have had the thyroid remnant successfully ablated, yet still harbor remnant thyroid tissue or residual tumor that was responsible for the serum Tg elevation.

An important caveat is that serum Tg measurements may be unreliable if antibodies to Tg are present above a certain level. In a first analysis of Tg, measurements were excluded if antibodies to Tg were present at 30 units/mL or above, which is a level justified by the central laboratory. A second analysis was prepared using a cut-off of 5 units/mL, which is the level recommended by the Tg kit manufacturer. Overall, serum samples for Tg measurements were collected from 48 patients at both Baseline and follow-up.

Tg Analysis Using Cut-Off for Tg-Antibodies of 30 units/mL
In the former Hypothyroid and Euthyroid groups, there were 20 and 25 patients, respectively, who had evaluable serum Tg levels after Thyrogen stimulation (Day 5). Data were not available from 3 patients: 2 patients had Tg antibodies above 30 units/mL and a third patient had their second laboratory sample appropriated at the local hospital for a different medical routine care purpose, rather than sent to the central laboratory. The mean stimulated Tg values were 0.6 ng/mL and 0.2 ng/mL in the former Hypothyroid and Euthyroid groups, respectively.

In this study, a Thyrogen-stimulated serum Tg level < 2 ng/mL was chosen as the criterion for remnant ablation success. Given this criterion, 95% and 96% of the patients in the former Hypothyroid and Euthyroid groups, respectively, had been ablated. If a serum Tg cut-off of 1 ng/mL is chosen as the critical level, then 90% and 92% of the patients in the former Hypothyroid and Euthyroid groups, respectively, are considered to be ablated. If the 9 patients who received additional ^{131}I therapy during the period between the two studies are excluded from this analysis (because the additional therapy would have made low levels of Tg easier to achieve), then a stimulated Tg level < 2 ng/mL occurred in 16/16 patients (100%) in the former Hypothyroid group and in 22/22 patients (100%) in the former Euthyroid group.

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Tg Analysis Using Cut-Off for Tg-Antibodies of 5 units/mL

After Thyrogen stimulation, serum Tg levels could be assessed in 37 patients. Mean Tg levels increased from 0.0 ng/mL at Baseline to 0.7 ng/mL in the former Hypothyroid group, and from 0.0 ng/mL to 0.2 ng/mL in the former Euthyroid group.

Thus, in spite of the previously described caveats about using a stimulated serum Tg as a marker for the presence of a normal thyroid remnant, use of this marker resulted in successful ablation in 94% and 95% of the evaluable patients in the former Hypothyroid and Euthyroid groups, respectively.

Excluding those patients who received additional ^{131}I therapy during the period between the two studies, then all (100%) patients who had antibody levels ≤ 5 units/mL (14/14 patients in the former Hypothyroid group and 18/18 patients in the former Euthyroid group) had stimulated Tg levels < 2 ng/mL.

Safety Results:

Treatment with Thyrogen during this follow-up study was well tolerated. There were no deaths, SAEs or withdrawals due to AEs reported during the conduct of this study.

During the 28-day Pre-treatment (Screening) period, only 3 AEs (anxiety, skin lesion and urticaria) were observed, among 2 patients. During the 5-day study period, 2 patients (8.7%) in the former Hypothyroid group and 6 patients (21.4%) in the former Euthyroid group experienced at least 1 treatment-emergent AE. Treatment-related AEs were reported in 3 patients (10.7%), all in the former Euthyroid group. All treatment-emergent AEs resolved during the course of the study, except for 1 AE of mild headache that was considered to possibly be related to treatment. Because most (48/51; 94%) patients in this follow-up study received Thyrogen, apparent differences between the former Hypothyroid and Euthyroid groups from the THYR-008-00 study are not considered to be clinically meaningful. No patients experienced severe treatment-emergent AEs during this 5-day follow-up study.

Apparent differences between the former Hypothyroid and Euthyroid groups during this follow-up study in the proportion of patients with treatment-emergent AEs (8.7% and 21.4%, respectively), and in the frequency of all AEs and treatment-related AEs, are not considered to be clinically meaningful, because a median of 3.7 years (range 3.4 to 4.4 years) have passed since the end of the THYR-008-00 study, and all patients in this follow-up study received Thyrogen. These differences are not believed to be due to whether the patients received Thyrogen (Euthyroid group) or not (Hypothyroid group) during the THYR-008-00 study, but perhaps to slight group differences in patient health history. Due to the relatively small numbers of patients in each group, it is difficult to assign group-related causality since results from only a few patients may skew the results for a group.

Mean TSH and free T4 values were similar for both groups at Screening, and although several TSH and free T4 values were out of range for both groups, none were considered to be clinically significant.

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Conclusions: [redacted]		