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NAME OF SPONSOR/COMPANY:

Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142

TITLE OF STUDY:

Protocol TSH95-0101: A Study of the Safety and Efficacy of Thryogen® (recombinant human TSH) in Detecting Well-Differentiated Thyroid Cancer by Radioiodine Whole Body Scanning and Thyroglobulin Testing

INVESTIGATORS AND STUDY CENTER(S)

This was a multinational, multicenter study conducted at 14 sites in both the United States (US) and Europe (EU).

STUDIED PERIOD

First patient enrolled: 8 November 1995
Late patient completed: 4 April 1997

PHASE OF DEVELOPMENT

Phase 3, Confirmatory

OBJECTIVES
Primary Objectives

- Confirm that Thyrogen® is safe and effective in providing adequate thyroid stimulating hormone (TSH) stimulation for the detection of post-thyroidectomy remnants and well-differentiated thyroid cancer by diagnostic radioiodine (^{131}I) imaging.
- Determine the superior Thyrogen® dosing regimen for providing adequate TSH stimulation for the detection of post-thyroidectomy remnants and well-differentiated thyroid cancer by diagnostic ^{131}I imaging.
- Confirm that patients experience fewer hypothyroid signs and symptoms after Thyrogen® administration than during the thyroid hormone suppression therapy (THST) withdrawal as measured by the Billewicz Scale.

Secondary Objectives

- Examine the benefit of TSH stimulation provided by Thyrogen® on the diagnostic utility of thyroglobulin (Tg) testing, both alone and in combination with diagnostic ^{131}I imaging, to detect thyroid remnants and thyroid cancer in patients who have had a total or near-total thyroidectomy.
- Establish the kinetic profile of the serum Tg response after Thyrogen® administration in patients capable of a Tg response.
- Collect additional safety data on patients with thyroid cancer following the administration of Thyrogen®.
- Evaluate patient-reported quality of life (QOL) after Thyrogen® administration in comparison to QOL during the TSH withdrawal (Hypothyroid) phase using the Standard Form-36 (SF-36) QOL scale.

METHODOLOGY

This study was a multi-center, open-label, randomized, 2-arm, parallel study that was designed to confirm that Thyrogen® is safe and effective when used as an adjunct to diagnostic ^{131}I imaging and Tg testing for detection of thyroid cancer. To study safety and efficacy, this study compared the whole-body scan (WBS) and Tg level obtained during TSH stimulation to the

WBS and Tg level obtained following THST withdrawal. Patients were enrolled into Arm I or Arm II of the study, either at the time of initial WBS or following a total or near-total thyroidectomy (when scheduled for ^{131}I imaging and a Tg test for the ongoing monitoring of their thyroid cancer). While patients remained on THST with suppressed endogenous serum TSH levels $\leq$ 0.5 mU/L, single 0.9 mg doses of Thyrogen® were administered as intramuscular (IM) injections according to the dosing regimen of the study arm (Thyrogen® Phase). The 2 dosing regimens were Arm I: 0.9 mg IM every 24 hours for 2 doses; and Arm II: 0.9 mg IM every 72 hours for 3 doses. Twenty-four hours after the final Thyrogen® dose, patients received a diagnostic activity of 4 mCi (±10%) (148 MBq) ^{131}I and underwent diagnostic scanning 48 hours later. Tg levels were measured at 1, 2, 3, and 7 days after the final injection of Thyrogen® in all study patients. Subsequently, the patients remained on THST for 2 additional weeks before being withdrawn for the period required for endogenous TSH levels to rise $\geq$ 25 mU/L (Hypothyroid Phase). Patients had a Tg level measurement and were then given the same diagnostic activity of 4 mCi (±10%) (148 MBq) ^{131}I and underwent diagnostic scanning 48 hours later. An assessment of hypothyroid symptomology was performed during the Pre-Treatment phase, after Thyrogen® administration, and after THST withdrawal using 2 validated QOL instruments.

NUMBER OF PATIENTS (PLANNED AND ANALYZED)

The number of patients planned was 254; the number analyzed was 220.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

All patients had a history of well-differentiated thyroid cancer (and were scheduled for diagnostic ^{131}I imaging and a Tg test). These included patients being scanned for the first time after a total or near-total thyroidectomy and patients who were returning as part of the ongoing monitoring of their cancer. All patients who had recently undergone a total or near-total thyroidectomy had surgery at least 6 weeks before study enrollment. It had been at least 4 months since ^{131}I ablation or ^{131}I therapy. Patients with non-thyroidal conditions known to decrease radioiodine uptake (e.g., congestive heart failure) or to cause false-positive radioiodine scans were excluded. Patients who were taking drugs that could affect thyroid function were also excluded. At enrollment, suppression of patients' TSH levels ($\leq$0.5 mU/L) by THST was confirmed. Additionally, for the Tg analysis, patients were required to be successfully ablated and Tg antibody negative.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION

Thyrogen® (thyrotropin alfa), 0.9 mg by IM injection.

DURATION OF TREATMENT

Arm I: 0.9 mg IM every 24 hours x 2 doses
Arm II: 0.9 mg IM every 72 hours x 3 doses

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION

Thyrogen®, 0.9 mg, was administered daily for 2 days via IM injection while patients were continuing their THST. Forty-eight hours after ^{131}I, patients returned for a WBS (Thyrogen® scan). After the Thyrogen® scan, patients continued on THST for at least 2 weeks to allow for TSH levels to return to pre-Thyrogen® treatment levels. The patient was withdrawn from this therapy for a minimum of 2 weeks until adequate levels of endogenous TSH ($\geq$25 mU/L) for a WBS were reached.

Subsequently, the same tracer ^{131}I dose (4 mCi) was used as the Thyrogen® scan was administered and a second WBS (Withdrawal scan) was performed 48 hours later.

CRITERIA FOR EVALUATION
Criteria for Evaluation – Efficacy
Anterior and posterior WBS at 48 hours after ^{131}I administration were evaluated for the presence of post-thyroidectomy thyroid remnants or well differentiated thyroid cancer. Evaluations were made by the independent reviewers using the uptake classification system developed for this study. The consensus of the independent reviewers was used for the efficacy analysis.

The primary efficacy analysis was a comparison of the uptake classification rating for the 48-hours WBS from each of the 2 scan series.

Criteria for Evaluation – Safety
Vital signs, hematologic signs, blood chemistry, development of antibodies to Thyrogen®, and adverse events (AEs) were evaluated for safety.

STATISTICAL METHODS
Demographic and Baseline characteristics are presented using descriptive statistics. Treatment group comparisons were made using analysis of variance (ANOVA) adjusting for centers. Comparisons of treatment arms for nominal categorical variables (e.g., sex) were made using the Cochran-Mantel-Haenszel test to allow adjustment for center effects.

Statistical Methods – Efficacy
For statistical analysis of the WBS, the proportion of patients in each uptake classification was presented with a point estimate and a 95% confidence interval (CI) using the Fleiss formula. In addition, a 2-tailed sign test was performed to test whether discordances significantly favored the Thyrogen® Phase scan or the Hypothyroid Phase scan. The 2-tailed Fisher's exact test was used to determine whether Arm II was significantly different from Arm I.

Descriptive statistics of the kinetic profile of the Tg were presented by study day and for each treatment arm. Treatment arm comparisons were performed using ANOVA on the change of Tg from Baseline (Day-7-Day0) for the common days only (1, 2, 3, and 7 days after final injection of Thyrogen®).

In the analysis of the diagnostic utility of a Thyrogen® Phase scan alone, a Thyrogen® Tg test alone, and the combination of the 2 methods together in the diagnosing the presence of tissue thyroid origin, a 95% CI for the sensitivity and specificity was presented using the Fleiss formula.

Hypothyroid Signs and Symptoms (Billewicz Scale and SF-36 Instrument): median change in signs and symptoms from Baseline to the Thyrogen® Phase scan were compared to median change from Baseline to the Hypothyroid Phase scan using the Wilcoxon Signed Rank test for within-treatment arm comparison and the Mann-Whitney test for comparisons between-treatment arms.

The mean thyroid percent ^{131}I uptake measured at the time of the Thyrogen® Phase scan was compared to the mean thyroidal percent ^{131}I uptake measured at the time of the Hypothyroid Phase scan using the Wilcoxon Sign Rank test within each treatment arm.

Statistical Methods – Safety
All safety data were summarized for the safety population. All AEs and serious adverse events (SAEs) were tabulated by body system, preferred term, relationship to study drug, and severity. In the event that AEs were reported more than once, the most extreme level of severity and relationship to treatment was tabulated in the summary tables.

SUMMARY / CONCLUSIONS
In the Intent to Treat (ITT) population, 142 patients had papillary thyroid cancer, 40 patients had papillary/follicular variant thyroid cancer, 39 patients had follicular thyroid cancer, and 8 patients had Hürthle cell thyroid cancer. Of 229 patients, 49 (Arm I {19 patients}; Arm II {30 patients}) had metastatic disease detected during the study.

Summary – Efficacy
Diagnostic ^{131}I imaging with Thyrogen® Compared to Withdrawal: In Arm I scans evaluated by the independent reviewers (IRs), the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 104/113 (92.0%) patients. The Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 110/113 (97.3%) patients. The Thyrogen® Phase and Hypothyroid Phase scans showed a higher uptake classification than the Thyrogen® Phase scans.

In Arm II scans evaluated by the IRs, the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 99/107 (92.5%) patients. Conversely the Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 102/107 (95.3%) patients. The scan pairs were concordant in 94/107 (87.9%) cases. Of the 13/107 (12.1%) patients with discordant scans, 5 patients' Thyrogen® Phase scans showed a higher uptake classification than the Hypothyroid Phase scans, and 8 patients' Hypothyroid Phase scans showed a higher uptake classification than the Thyrogen® Phase scans.

Scan Evaluable Intent to Treat Population: In Arm I scans evaluated by the IRs, the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 104/113 (92.0%) patients. The Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 110/113 (97.3%) patients. The Thyrogen® Phase and Hypothyroid Phase scans were concordant in 101/113 (89.4%) patients.

In Arm II scans evaluated by the IRs, the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 99/107 (92.5%) patients. The Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 102/107 (95.3%) patients. The scan pairs were concordant in 94/107 (87.9%) cases.

Patients with Positive Diagnostic Scans: Arm I, the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 39/48 (81.3%) cases. The Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 45/48 (93.8%) cases.

In Arm II the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 52/60 (86.7%) cases. The Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 55/60 (91.7%) cases.

Patients with Uptake Limited to the Thyroid Bed: In Arm I, the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 33/39 (84.6%) cases. The Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 36/39 (92.3%) cases.

In Arm II the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 38/44 (86.4%) cases. The Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 41/44 (93.2%) cases.

Patients with Uptake Outside of the Thyroid Bed: In Arm I the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 6/9 (66.7%) patients. The Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 9/9 patients (95% C.I. = 62.9 -100%).

In Arm II the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 14/16 (87.5%) cases (95% C.I. = 60.4 – 97.8%). The Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 14/16 (87.5%) cases (95% C.I. = 60.4 – 97.8%).

Patients with Confirmed Metastatic Thyroid Cancer: In Arm I the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase Scan in 15/19 (79.8%) patients. Conversely the Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 18/19 (94.7%) patients.

In Arm II the Thyrogen® Phase scan showed a higher or concordant uptake classification to the Hypothyroid Phase scan in 26/30 (86.7%) patients. The Hypothyroid Phase scan showed a higher or concordant uptake classification to the Thyrogen® Phase scan in 29/30 (96.7%) patients.

Kinetics of the Tg Response to Thyrogen®: For Arm I, the highest Tg levels were achieved more than 24 hours after the final Thyrogen® injection, with mean values increasing for the first 3 days and declining by the seventh day. Arm II results were consistent with Arm I and indicated that there is little difference in the Thyrogen®-stimulated Tg levels at 1, 2, and 3 days after the final Thyrogen® injection. For both study arms, Tg levels achieved 2 to 6 weeks after THST withdrawal were consistently higher than levels 1 to 9 days after TSH stimulation by Thyrogen®.

Diagnostic Utility of Tg Testing with Thyrogen® and ^{131}I imaging: Seventy-nine patients from Arm I were eligible for this diagnostic utility analysis. Fifty (63%) of these 79 patients had the presence of thyroid remnants or cancer identified by the reference standard. Within this group of 79 patients, if a patient had a Tg level $\geq$ 3 ng/mL while euthyroid on THST and had either a Hypothyroid Phase Tg < 10 ng/mL or a positive Hypothyroid scan, then this patient was rated as a “true positive.” If a patient had a Tg level $\geq$ 3 ng/mL while euthyroid on THST but had both a Hypothyroid Phase Tg level < 10 ng/mL and a negative Hypothyroid Phase scan, then this patient was rated as a “false positive.”

Within this group of 79 patients, if a patient had a Tg level < 3 ng/mL while euthyroid on THST, and had both a Hypothyroid Phase Tg level < 10 ng/mL and a negative Hypothyroid scan, then this patient was rated as a “true negative.” If a patient had a Tg level < 3 ng/mL while euthyroid on THST but had either a Hypothyroid Phase Tg $\geq$ 10 ng/mL or a positive Hypothyroid Phase scan, then this patient was rated as a “false negative.”

Within this group of 79 patients, 19 patients were rated as true positives, no patients were rated as false positives, 29 were rated as true negatives, and 31 were rated as false negatives. Therefore, a Tg test while patients were euthyroid on THST (using the Tg level of 3 ng/mL) correctly detected 19/50 patients considered to have thyroid remnant or cancer. A Tg test while patients were euthyroid on THST (using the Tg level of 3 ng/mL) did not detect 31/50 patients considered to have thyroid remnant or cancer.

Sensitivity is determined by the ratio of true positives to the sum of true positives and false negatives. In this group of patients the ratio is 19/(19 + 31) = 38%. As the number of false negative results decreases, the sensitivity becomes better.

Negative predictive value is determined by the ratio of true negatives to the sum of true negatives and false negatives. In this group of patients the ratio is 29/(29 + 31) = 48%. As the number of false negative results decreases, the negative predictive value becomes better.

Specificity is determined by the ratio of true negatives to the sum of true negatives and false positives. In this group of patients the ratio is 29/(29 + 0) = 100%. As the number of false positive results decreases, the specificity becomes better.

Positive predictive value is determined by the ratio of true positives to the sum of true positives and false positives. In this group of patients the ratio is 19/(19 + 0) = 100%. As the number of false positive results decreases, the positive predictive value becomes better.

Accuracy is determined by the ratio of the sum of true positives and true negatives to the total number of eligible patients. In this group of patients the ratio is (19 + 29)/79 = 61%. As the number of true positive and true negative results increases, the accuracy of the test increases.

Hypothyroid Signs and Symptoms (Billewicz Scale): Significant ($p<0.05$) paired differences were observed for hypothyroid signs and symptoms between the Thyrogen® Phase and Hypothyroid Phase. The differences favored the Thyrogen® Phase, indicating that patients who were administered Thyrogen® while clinically euthyroid on THST experienced fewer hypothyroid signs and symptoms than patients who became clinically hypothyroid while undergoing THST withdrawal.

Quality of Life (SF-36 Instrument): Significant ($p<0.05$) paired differences were observed for hypothyroid signs and symptoms between the Thyrogen® Phase and Hypothyroid Phase. The differences clearly favored the Thyrogen® Phase across all eight domains of the SF-36, indicating that patients who were administered Thyrogen® while clinically euthyroid on THST experienced a better QOL than patients who became clinically hypothyroid while undergoing THST withdrawal. The statistically significant differences between the study phases favored the Thyrogen® Phase.

Evaluation of Percent ^{131}I Uptake: There was no difference between 48-hour uptake of the Thyrogen® Phase scan compared to 48-hour uptake of the Hypothyroid Phase scan in Arm I. However, in Arm II, the Hypothyroid Phase scan uptake was higher than in Arm I ($p<0.050$, Wilcoxon Signed Rank Test) with uptake measured by a thyroid probe. When making the same comparison using 48-hour uptake measured by region of interest (ROI) techniques, there were no differences observed in either Arm. However, interpretation of these data is limited because of the high proportion of patients who had very minimal thyroid bed uptake.

Summary - Safety Results:
Adverse Events: No deaths were reported during the study. A total of 4 patients reported 8 SAEs (Arm I: 3 patients; Arm II: 1 patient), which were considered to be not related to Thyrogen® by the treating physician. All patients reporting SAEs recovered. During the entire study (i.e., Thyrogen® Phase and Hypothyroid Phase), 103/229 patients reported a total of 207 AEs. In Arm I during the Thyrogen® Phase, 46/117 patients reported a total of 73 AEs. In Arm II, 33/112 patients reported a total of 69 AEs. During the Hypothyroid Phase, 43/229 patients reported a total of 65 AEs. During the Thyrogen® Phase, the most common AEs included headache, nausea and vomiting, asthenia, paresthesia, and pain. In general, these treatment-emergent AEs were mild. No statistical difference ($p=0.076$, paired t-test) was found between Arm I and Arm II in the occurrence of treatment-emergent AEs. During the Hypothyroid Phase, the most frequently reported treatment-emergent AEs were hypercholesterolemia, hyperlipidemia, and elevated creatinine levels. These treatment-emergent AEs were generally mild and are expected in hypothyroid patients. .

Vital Signs, Hematology Parameters, Blood Chemistry Parameters: Greater differences from Baseline values were observed during the Hypothyroid Phase than during the Thyrogen® Phase. In general, there was no clear effect of Thyrogen® administration on these parameters.

Patient Immune Response (Antibody development) to Thyrogen®: The results of testing for anitbodies to Thyrogen® indicated that no patients developed antibodies specific to Thyrogen®.

Based on Report Prepared on: 16 October 1997
Synopsis Prepared on: 20 September 2005