CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020898

STATISTICAL REVIEW(S)

APR 20 1998

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-898

SPONSOR: Genzyme Corporation

DRUG: Thyrogen® (thyrotropin alfa)

DRUG CLASS: 1P

INDICATION(S): For use as an alternative to thyroid hormone withdrawal for radioiodine imaging in combination with thyroglobulin testing conducted for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients. It is a management option for patients maintained on thyroid hormone in order to avoid the morbidity associated with hypothyroidism. Thyrogen® is also indicated for the enhancement of the sensitivity of a serum thyroglobulin test performed in patients on hormone suppression therapy.

DOCUMENTS REVIEWED: Volumes 1.1, 1.47-1.64; other materials submitted by the sponsor are letter dated 1-16-98, 1-28-98, 2-13-98 (2 jackets), 2-19-98, 2-26-98, and 3-16-98.

DATES: **Date received by Medical Division, HFD-510 (Stamp Date):** December 15, 1997
Date received by Division of Biometrics, HFD-720: February 16, 1998
User Fee Date: June 15, 1998

MEDICAL REVIEWER: Jean Temeck, M.D., HFD-510

STATISTICAL REVIEWER: Sonia Castillo, Ph.D., HFD-720

Major Review Issues:

- Blinded evaluation was based on a paired read instead of a separate and independent read of the Thyrogen and Withdrawal scans.
- Studies were not independent; the same three blinded readers and 7 of the same Principal Investigators were used in both studies.
- Primary endpoint was mis-specified.
- The mediation panel for image evaluation used additional information.
- Scans for the blinded reads were pre-selected as being adequate for evaluation by the study monitor without any criteria specified.
- Multiple *post hoc* analyses were submitted.
- Multiple standards of truth were utilized in the ROC and diagnostic utility analyses.
- Withdrawal scan results were part of the standard of truth (in the ROC analyses) in addition to being the comparator.

Study TSH92-0601: **A Study of the Safety and Effectiveness of Thyrogen *AND***
Study TSH95-0101: **A Study of the Safety and Efficacy of Thyrogen (recombinant human TSH) in Detecting Well-Differentiated Thyroid Cancer by Radioiodine Whole-Body Scanning and Thyroglobulin Testing.**

1.0 BACKGROUND INFORMATION

The treatment of a patient diagnosed with well-differentiated thyroid cancer (papillary, follicular, and Hürthle cell) consists of a total or near-total thyroidectomy and a whole body scan (WBS) with radioactive iodine (^{131}I) to find remnant tissue and/or metastases left after surgery. If significant remnants are present or if metastatic cancer is found, the patient receives a therapeutic dose of ^{131}I to ablate remnant tissue and cancer. After this initial treatment is completed, the patient begins hormone replacement therapy consisting of an exogenous supply of one of two hormones normally produced by the thyroid. Sufficient levels of this hormone act in a negative feedback loop to suppress thyroid stimulation hormone (TSH) production by the pituitary gland. The association between thyroid hormone replacement therapy and suppression of thyroid tumor growth has been documented. Physicians choose to suppress TSH production at levels below detection to avoid the chance of stimulating growth of any remaining thyroid cancer. Therefore, replacement therapy is also called thyroid hormone suppression therapy (THST).

Patients are then monitored closely for recurrent cancer or metastatic spread. The two most commonly used methods for detecting thyroid cancer in thyroidectomy patients are diagnostic radioiodine (^{131}I) imaging and serum thyroglobulin (Tg) testing. Diagnostic ^{131}I imaging can indicate the extent and localization of the tumor. Tg testing is very useful in detecting the presence of cancer that is not yet visible by diagnostic ^{131}I imaging or cancerous tissue that does not uptake the ^{131}I. This is true only if the patient is successfully ablated because Tg levels should not be measurable in a patient who has undergone successful thyroidectomy and ^{131}I ablation. Each method is effective at detecting cancer, but the clinical community generally agree that using both together is superior to using either method alone.

Both the diagnostic ^{131}I imaging and Tg testing detection methods rely on elevated endogenous TSH levels. Diagnostic ^{131}I imaging relies on uptake of ^{131}I by thyroid or cancerous cells stimulated by TSH and Tg testing relies on a mechanism where TSH-stimulated thyroid cells synthesize and release Tg. Current medical practice is to withdraw patients from THST in order to elevate endogenous TSH levels, which subjects patients to a prolonged period of hypothyroidism (2-6 weeks off THST for elevation of endogenous TSH and 3-4 weeks for return to appropriate thyroid hormone level after withdrawal from THST).

of life. The main symptoms include mental and physical slowing with memory defect and poor attention span, fatigue, cold intolerance, nausea, constipation, weight gain, decreased libido and irritability.

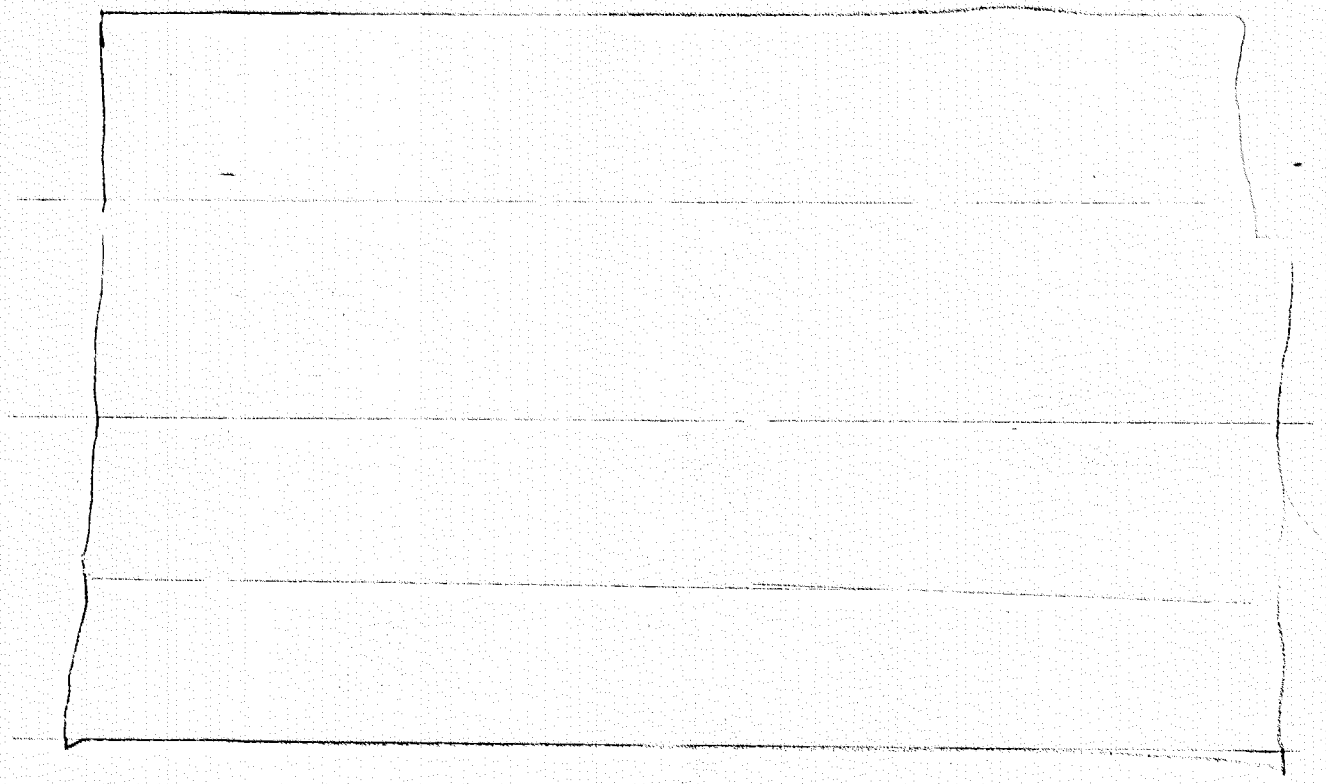


Table 2.1 gives an overview of the two studies for the indication sought. This review will present

Table 2.1
Overview of Studies TSH92-0601 and TSH95-0101

Study	No. of Centers	Design[1]	Regimens of Intramuscular Injection Dose of Thyrogen	Type of Control	Sample Size: -Total (Treated)	Subgroups: - M/F Treated
TSH92-0601	11	OL, SB, 1A	Two 0.9 mg doses every 24 hours	Baseline on THST	152 (152)	46 / 106
TSH95-0101	14	OL, SB, 2A, R, P	a) Two 0.9 mg doses every 24 hours b) Three 0.9 mg doses every 72 hours	Baseline on THST	a) 123 (117) b) 131 (112)	81 / 148

[1] *OL: Open-label, SB: Single-blind Dose Administration, R: Randomized Dose Regimen, 1A: Single Arm, 2A: Two Arm, P: Parallel Dose*

an overview of each study, describe the study conduct, safety and efficacy data collected, the sponsor's primary efficacy analyses and results, this reviewer's evaluation of the study and sponsor's analyses, and this reviewer's conclusions.

3.0 OBJECTIVES OVERVIEW

3.1 Study TSH92-0601

The primary objective of this Phase 3 clinical trial was to determine the safety and effectiveness of Thyrogen when used as an adjunct to whole body scanning for the detection of remnants and metastases.

The three secondary objectives were the following:

- To determine the percent ^{131}I uptake in all foci indicative of remnant and thyroid cancer tissue measured at the time of each scan.
- To assess the presence or absence of normal sites of ^{131}I concentration in the sinus, salivary glands, GI tract, and bladder.
- To confirm that patients experience fewer hypothyroid symptoms after Thyrogen administration than during the THST withdrawal period using the Billewicz Scale and the short form Profile of Mood States (POMS) Scale.

3.2 Study TSH95-0101

The three primary objectives of this Phase 3 clinical trial were the following:

- To confirm that Thyrogen is safe and effective as an exogenous source of TSH in providing adequate TSH stimulation for the detection of post thyroidectomy remnants, well-differentiated thyroid cancer and metastases when used as an adjunct to whole body scanning for the detection of remnants and metastases.
- To determine the superior Thyrogen dosing regimen for providing adequate TSH stimulation for the detection of post thyroidectomy remnants, well-differentiated thyroid cancer and metastases by a WBS.
- To confirm that patients experience fewer hypothyroid symptoms after Thyrogen administration than during the THST withdrawal period using the Billewicz Scale.

The four secondary objectives were the following:

- To examine the benefit of TSH stimulation provided by Thyrogen on the diagnostic utility of Tg testing, both alone and in combination with a WBS, to detect well-differentiated thyroid cancer in patients who have had a total or near-total thyroidectomy and have received radioiodine ablation or sufficient surgery to preclude interference from any functional remnant thyroid.
- To establish the kinetic profile of the serum Tg response after Thyrogen administration in patients capable of Tg response.
- To collect additional safety data on patients with well-differentiated thyroid cancer following the administration of Thyrogen.
- To evaluate patient reported quality of life (QOL) after Thyrogen administration in comparison to quality of life during the THST withdrawal period using the SF-36 QOL Scale.

The sponsor claimed that with the use of Thyrogen, patients can remain euthyroid on their hormone suppression therapy (THST) during diagnostic testing and, therefore, avoid the clinical effects of hypothyroidism. Additionally, Thyrogen can improve the sensitivity of Tg testing in patients maintained on THST, as an elevated TSH level is necessary to induce Tg synthesis and release.

4.0 STUDY POPULATION

In both Study TSH92-0601 and Study TSH95-0101, patients were enrolled when they were: 1) scheduled for an initial whole body scan (WBS) following thyroidectomy and prior to ^{131}I ablation

to detect the presence of remnant thyroid tissue or metastatic cancer, or 2) scheduled for a post-ablation scan and a Tg test for the ongoing monitoring of their thyroid cancer. Patients who met all the inclusion/exclusion criteria were enrolled.

Study TSH92-0601 was an 11 center, open-label, one arm study.

Study TSH95-0101 was a 14 center, open-label, randomized, two arm, parallel study. It was anticipated that approximately 55% of study patients would have post thyroidectomy thyroid remnants, recurrent cancer, and/or local or distant metastases identifiable by WBS. Within this population, a portion of the patients, suspected to have metastatic disease outside the thyroid bed, was selectively enrolled in order to have a sufficient number of patients to evaluate the efficacy in the normally small subset of patients with metastatic disease. Patients who were enrolled were then randomized to one of the two dosing arms of the study from a centralized list in the custody of the Genzyme study monitors. Assignment was given in sequential order from the computer-generated master randomization list for each site. Each patient assignment was unique and was not reassigned to any other patient.

4.1 Inclusion Criteria

Inclusion criteria that were the same for both studies were adult male and female patients at least 18 years of age with well-differentiated thyroid cancer, and who were committed to follow the protocol requirements as evidenced by written, informed consent. Also, those patients enrolled following recent thyroidectomy must have completed a minimum of 1 calendar month of (THST) prior to entry into the study. All patients must have been on THST sufficient to suppress serum TSH levels to ≤0.5 mU/L as confirmed by the investigational site's laboratory within 7 days prior to the first dose of Thyrogen.

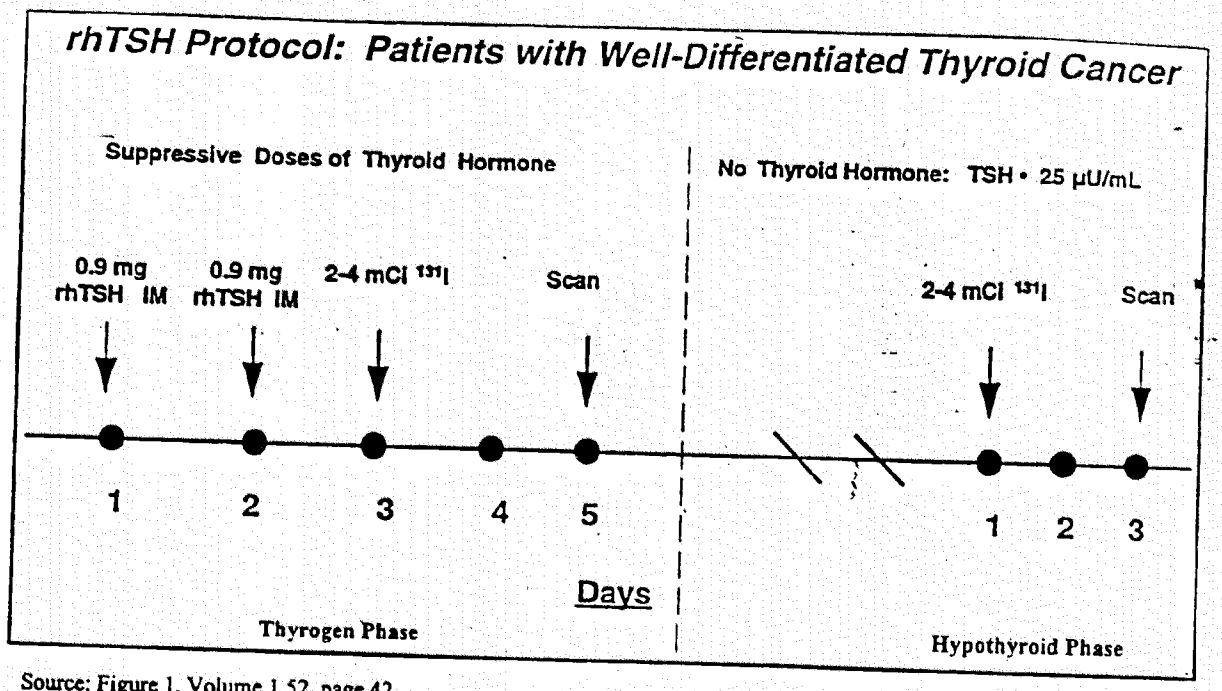
The inclusion criteria for Study TSH95-0101 included that patients must have undergone total or near-total thyroidectomy; be at least 6 weeks post thyroidectomy or other most recent thyroid surgery; and be at least 4 months post ^{131}I ablation or ^{131}I therapy. In addition, patients were eligible for this study if they participated in a prior Thyrogen study(ies).

4.2 Exclusion Criteria

Key exclusion criteria for both studies were patients with undifferentiated thyroid cancer or lymphoma of thyroid and patients for whom radioiodine scan is contraindicated because withdrawal from THST is not an option due to pituitary dysfunction or other compelling medical reasons.

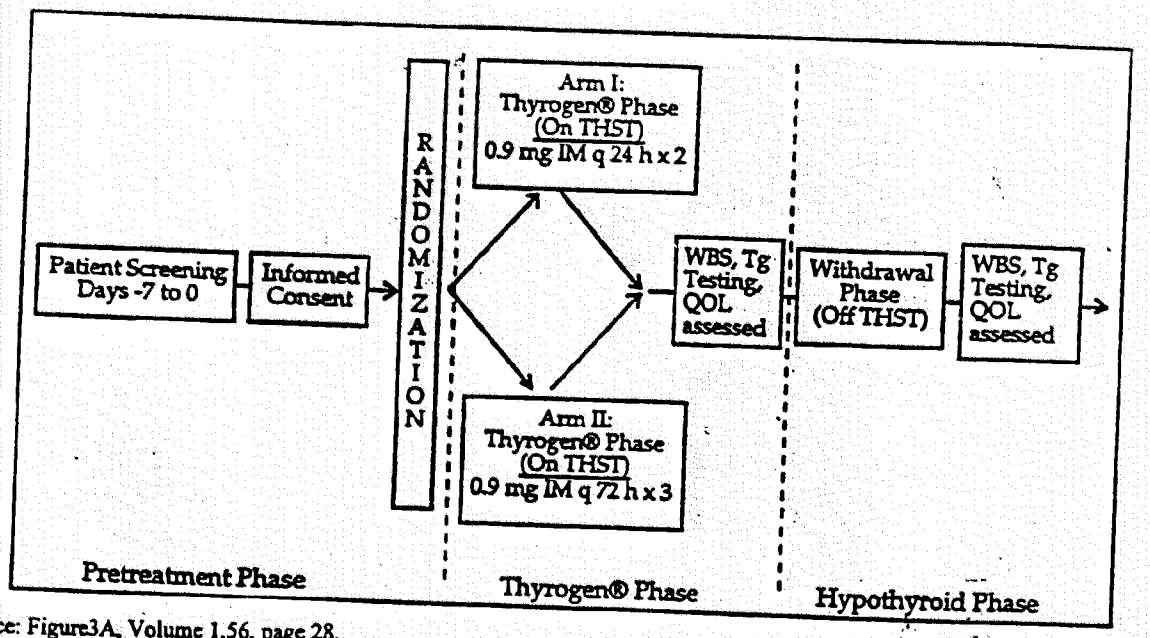
Other exclusion criteria for Study TSH92-0601 can be found in Volume 1.52, Section 3.2 of the protocol on pages 101-102, and for Study TSH95-0101 can be found in Volume 1.58, Section 4.2 of the protocol on pages 26 to 27.

Figure 1: Study TSH92-0601 Time Line



Source: Figure 1, Volume 1.52, page 42.

Figure 2: Study TSH95-0101 Time Line



Source: Figure3A, Volume 1.56, page 28.

5.0 STUDY DESIGN AND PROCEDURES

In both studies, patients served as their own control. All patients received Thyrogen first followed by THST withdrawal. Thyrogen was administered at the investigational site via intramuscular injection into the patient's buttocks. A WBS was performed after Thyrogen administration and during THST withdrawal. Measurements were made at baseline, while the patient was euthyroid on THST, after receiving Thyrogen while euthyroid, during the washout period, and at withdrawal while hypothyroid. Time lines for both studies are presented in Figures 1 and 2.

5.1 Study TSH92-0601

5.1.1 Study Drug Dosing Regimen and Administration

The dosing regimen for Study TSH92-0601 was one 0.9 mg injection of Thyrogen, every 24 hours for two injections total.

5.1.2 Baseline Procedures

Each patient underwent a baseline evaluation that collected information on demographics, medical history, THST regimen, and concomitant medication. If the patient was female with reproductive potential, a negative pregnancy test at the time of study entry was documented. Four separate blood samples for hematology, blood chemistry, and patient immune response to Thyrogen were collected. No scans were performed during this period of the study. Hypothyroid symptoms were assessed using the physician rated Billewicz scale and the patient rated POMS scale.

5.1.3 Thyrogen Study Period Procedures

Throughout the Thyrogen study period, patients remained on their thyroid replacement therapy. Adverse events were monitored during the entire conduct of the study. Safety data collected at each study day included vital signs (temperature, blood pressure, pulse rate), and four separate blood samples drawn for hematology, blood chemistry, patient immune response to Thyrogen, and thyroid function tests. All blood samples were collected before receiving any ^{131}I and before any scanning was done.

Following the baseline evaluation, each patient received their 0.9 mg injections of Thyrogen according to their dosing regimen while still on THST. Twenty four hours after the final injection, the patient received a 2-4 mCi dose of radioiodine (^{131}I). Forty eight hours after ^{131}I administration, a second hypothyroid symptom and QOL assessment was made. The patient then had a WBS using a gamma camera that acquired anterior and posterior views.

5.1.4 Thyrogen Washout Period Procedures

Throughout the Thyrogen washout period, the patient continued with their THST regimen to allow their TSH levels to return to normal prior to discontinuing their THST. This period lasted from 10 to 11 days.

5.1.5 Withdrawal Study Period Procedures

Upon completion of the Thyrogen washout period, the patient was withdrawn from THST for an adequate time for endogenous serum TSH levels to increase to ≥25 mU/L as measured by the

investigational site's laboratory. This period lasted from 2 to 6 weeks, depending on the thyroid hormone replacement medication used by the patient.

Patients then received the same ^{131}I dose as used for the Thyrogen scan. Forty eight hours after ^{131}I - dosing, a third hypothyroid symptom and QOL assessment was conducted. Then the 48 WBS was performed using the same scanning procedures used for the 48 hour Thyrogen WBS.

Next, the Withdrawal scan and serum Tg level were evaluated at the investigational site and ^{131}I or other therapy was given if indicated. Patients who received radioiodine therapy may have undergone a post-therapy (^{131}I) scan one week later.

5.1.6 Thyroid Function Tests

Serum Tg and Tg auto-antibody levels were analyzed at the investigational site. The investigational site results may have been used by the treating physician for patient management.

5.1.7 Whole Body Scan Preparation for Blinded Readers

After collection by Genzyme, each WBS series (for Thyrogen and Withdrawal) was evaluated by someone at Genzyme to determine the presence of post thyroidectomy thyroid remnant, cancer recurrence or metastases. Initially an assessment of the technical quality and image resolution of each collective batch of films within the WBS series was made. Scans were judged as either adequate, sub optimal but interpretable, or inadequate and not interpretable. Scans determined to be inadequate were not reviewed further. All references to patient identity, institution, treatment, and time of conduct of the scans were concealed.

5.1.8 Blinded Read Procedure of Whole Body Scan

Each of three independent blinded readers is an expert in the field of radioiodine scanning of thyroid cancer. Readers were blinded to patient identity, institution, treatment, and time of conduct of the scans. Each blinded reader evaluated the scans independently of the other two readers. The rating specified by two or more readers (majority) of each scan study was the rating used for analysis.

Each blinded reader received a patient's Thyrogen and Withdrawal scans and was asked to evaluate each scan separately. The initial review consisted of the reader rating the technical quality and resolution of each film as adequate, suboptimal but interpretable, or inadequate. The reader documented the presence or absence of normal sites of radioiodine concentration observed on the scan. The reader then indicated if there was evidence of artifact or false positive scan. If this evidence was present, the reader indicated what he thought it might be and specified the location. Next, the images from each WBS were evaluated to determine whether or not there was uptake consistent with remnant tissue or cancer. The extent and location of uptake was rated for the stage of disease present using a cancer classification system (see Table 6.1). The reader also specified where the foci of uptake were observed on anatomical diagrams.

After completing the separate evaluation of each scan, the reader rated in a side-by-side (paired) manner each patient's Thyrogen and Withdrawal scans for "equivalency". The two scans were compared to determine if they both displayed the same extent of disease. Equivalent scans showed the same number and distribution of disease sites. When there was discordance within the scan pair,

the scan with a greater number and/or a more widespread distribution of disease sites was determined to be the superior scan.

Scan studies which revealed Stage 2, 3, or 4 disease were rated clinically equivalent if the scan pair showed the same number and distribution of disease sites. When uptake was limited to the thyroid bed, scan pairs were rated as equivalent provided the same number and distribution of lesions was observed, unless a large remnant may have absorbed a large amount of ^{131}I resulting in an image which may have obscured uptake in additional smaller sites. To discriminate between multiple foci within the neck, the image taken with the pinhole collimator was used, if available.

A consensus evaluation was provided if the readers needed more information to make a rating, the readers suspected an artifact or false positive focus of uptake, or all three readers disagreed in their rating of a scan pair. The three readers then met as a consensus panel and used extra views, post therapy scans, etc. as a mediator to complete their evaluation or to resolve significant differences of opinion.

5.2 Study TSH95-0101

5.2.1 Study Drug Dosing Regimens and Administration

The two dosing regimens for Study TSH95-0101 were: 1) for Arm I, one 0.9 mg Thyrogen injection every 24 hours for two injections total and 2) for Arm II, three 0.9 mg Thyrogen injections every 72 hours for three injections total.

5.2.2 Baseline Procedures

Each patient underwent a baseline evaluation that collected information on demographics, medical history, THST regimen, and concomitant medication. If the patient was female with reproductive potential, a negative pregnancy test at the time of study entry was documented. Four separate blood samples for hematology, blood chemistry, thyroid function tests (serum TSH, Tg, and Tg antibody level measurement), and patient immune response to Thyrogen were collected. No scans were performed during this period of the study. Hypothyroid symptoms were assessed using the physician rated Billewicz scale and the quality of life was assessed using the patient rated SF-36 QOL scale.

5.2.3 Thyrogen Study Period Procedures

Throughout the Thyrogen study period, patients remained on their thyroid replacement therapy. Adverse events were monitored during the entire conduct of the study. Safety data collected at each study day included vital signs (temperature, blood pressure, pulse rate), and four separate blood samples drawn for hematology, blood chemistry, patient immune response to Thyrogen, and thyroid function tests. All blood samples were collected before receiving any ^{131}I and before any scanning was done.

Following the baseline evaluation, each patient received their 0.9 mg injections of Thyrogen according to their dosing regimen while still on THST. Twenty four hours after the final injection, the patient received a 2-4 mCi dose (Study TSH92-0601) or 4 mCi dose (Study TSH95-0101) of radioiodine (^{131}I). Forty eight hours after ^{131}I administration, a second hypothyroid symptom and QOL assessment was made. The patient then had a WBS using a gamma camera that acquired

anterior and posterior views. Some sites may have conducted 72 hour scans, and, throughout the remainder of the Thyrogen study period, designated investigational sites conducted a quantitative ^{131}I dosimetry study and collected additional blood samples for this purpose.

5.2.4 Thyrogen Washout Period Procedures

Throughout the Thyrogen washout period, the patient continued with their THST regimen to allow their TSH levels to return to normal prior to discontinuing their THST. This period lasted from 10 to 11 days.

5.2.5 Withdrawal Study Period Procedures

Upon completion of the Thyrogen washout period, the patient was withdrawn from THST for an adequate time for endogenous serum TSH levels to increase to ≥25 mU/L as measured by the investigational site's laboratory. This period lasted from 2 to 6 weeks, depending on the thyroid hormone replacement medication used by the patient.

Patients then received the same ^{131}I dose as used for the Thyrogen scan. Forty eight hours after ^{131}I dosing, a third hypothyroid symptom and QOL assessment was conducted. Then the 48 WBS was performed using the same scanning procedures used for the 48 hour Thyrogen WBS. Thyroidal uptake measurements were done for all patients.

Next, the Withdrawal scan and serum Tg level were evaluated at the investigational site and ^{131}I or other therapy was given if indicated. It was required that any patient receiving radioiodine therapy or surgery undergo either a post-therapy scan or provide a histology report after surgery.

5.2.6 Thyroid Function Tests

Serum Tg and Tg auto-antibody levels were analyzed at a single, contracted central laboratory and, in addition, were analyzed at the investigational site. The investigational site results were used by the treating physician for patient management. The central laboratory results were used for the efficacy analyses. Central laboratory analysis was provided by the University of Southern California Endocrine Services Laboratory in Los Angeles, California.

5.2.7 Whole Body Scan Preparation for Blinded Readers

After collection by Genzyme, each WBS series (for Thyrogen and Withdrawal) was evaluated by someone at Genzyme to determine the presence of post thyroidectomy thyroid remnant, cancer recurrence or metastases. Initially an assessment of the technical quality and image resolution of each collective batch of films within the WBS series was made. Scans were judged as either adequate, sub optimal but interpretable, or inadequate and not interpretable. Scans determined to be inadequate were not reviewed further. All references to patient identity, institution, treatment, and time of conduct of the scans were concealed. The scan masking was done by Medical Development Quality Associates, a contract organization.

5.2.8 Blinded Read Procedure of Whole Body Scan

Each of three independent blinded readers is an expert in the field of radioiodine scanning of thyroid cancer. The same three blinded readers who evaluated the WBSs from Study TSH92-0601 were used. Readers were blinded to patient identity, institution, treatment, and time of conduct of the