THYR-007-00: Thyrogen® Compassionate Use Program Retrospective Data Collection and Analysis Protocol for Canada/United States of America.

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Investigators and Study Center(s)

A total of 63 physicians in the USA and Canada contributed patients to the retrospective data collection.

Studied Period

This is a retrospective collection and analysis of data obtained from the Thyrogen® Compassionate Use Program, in which patients had been treated with Thyrogen® between 1995 and 2000.

Phase of Development

Phase 3

Objectives

The objective of this protocol was to collect retrospectively and analyze the safety and efficacy data obtained from consenting patients with differentiated thyroid cancer who participated in the Thyrogen® Compassionate Use Program.

Methodology

Study files were reviewed to identify all physicians who requested Thyrogen® in the Compassionate Use Program for its use with radioiodine for the ablation of thyroid remnants or metastatic disease. All physicians were contacted to verify treatment of their patients and to determine interest in participating in the retrospective data collection. These physicians were then asked to provide copies of the patient's signed informed consent form(s). The proper version of the consent form was required to be on file for each Thyrogen® treatment course prior to the patient's inclusion in the retrospective data collection. The proper version of the consent form provided permission to Genzyme and Regulatory Authorities to review the patient's medical records.

Retrospective Data Collection Case Report Forms were sent to all interested physicians who treated properly consented patients with Thyrogen® as an adjunct to radioiodine ablation therapy. Data monitoring and source document verification were performed at all participating sites.

Number of Patients (Planned and Analyzed)

Approximately 300 patients had been treated with Thyrogen® in the US or Canada as part of the Compassionate Use Program. The physicians who treated 115 of these patients agreed to participate in this retrospective data review.

Diagnosis and Main Criteria for Inclusion
Inclusion

Patients with the following characteristics were considered eligible for the Retrospective Data Collection effort in the Compassionate Use Program:

- Patients who provided written informed consent for the Thyrogen® Compassionate Use Program. In addition to granting permission to enroll in the study, the consent granted access to the patient's medical records for data inspection and monitoring by Genzyme Corporation.
- Patients in whom Thyrogen® was administered as an adjunct to radioiodine ablative therapy for remnant thyroid

tissue and/or metastatic disease.

Test Product, Dose, and Mode of Administration

Thyrogen® 0.9 mg was administered intramuscularly on 2 consecutive days.

Duration of Treatment

N/A.

Reference Therapy, Dose and Mode of Administration

N/A.

CRITERIA FOR EVALUATION
Safety

All safety data was summarized for safety population. All Thyrogen®-related adverse events (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. Treatment-emergent SAEs were defined as those events occurring up to 90 days following treatment.

Efficacy

The following efficacy variables were determined (parameters in the first 2 bullets were designated the primary endpoints):

- Percentage of patients with inability to increase endogenous thyroid stimulating hormone (TSH) in response to hypothyroidism, whose serum TSH levels rose to $\geq$25 mU/L after treatment with Thyrogen®.
- For patients enrolled to avoid specific potential life-threatening event(s) if withdrawn from thyroid hormone suppression therapy (THST), the percentage of these patients was determined in whom the administration of Thyrogen® and a therapeutic dose of ^{131}I was not associated with the pre-specified life-threatening event(s).
- Change from baseline in thyroglobulin (Tg) levels assayed at 3-, 6-, 9-, and 12-month follow-ups after Thyrogen® plus radioiodine treatment.
- Change from the most recent scans of the same type in overall scan results at follow-up after Thyrogen® plus radioiodine treatment was categorized as improved, worsened, or no change, as assessed by the Principal Investigator after retrospectively reviewing the patient's medical chart and relevant scans.
- Change (pre-treatment vs. post-treatment with Thyrogen® plus radioiodine) in central nervous system (CNS) symptomatology (including paralysis or hemiplegia and loss of feeling) was categorized as improved, worsened, or no change, as assessed by the Principal Investigator after retrospectively reviewing the patient's medical chart.
- Change (pre-treatment vs. post-treatment with Thyrogen® plus radioiodine) in respiratory symptomatology including airway obstruction, shortness of breath, and hemoptysis was categorized as improved, worsened, or no change, as assessed by the Principal Investigator after retrospectively reviewing the patient's medical chart.
- Change (pre-treatment vs. post-treatment with Thyrogen® plus radioiodine) in skeletal symptomatology, (including bone pain) was categorized as improved, worsened, or no change, as assessed by the Principal Investigator after retrospectively reviewing the patient's medical chart.
- Change (pre-treatment vs. post-treatment with Thyrogen® plus radioiodine) in global status of symptomatology was categorized as improved, worsened, or no change, as assessed by the Principal Investigator after retrospectively reviewing the patient's medical chart.
- Change (pre-treatment vs. post-treatment with Thyrogen® plus radioiodine) in global status of medical regimen for pain management was categorized as increased, decreased, or no change.

STATISTICAL METHODS
Safety

No formal hypothesis testing was performed on the safety data. All Thyrogen®-related AEs and 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.

Efficacy

All efficacy analyses were performed on the Intent-to-Treat (ITT) population. The primary assessments of interest also were performed on the Per-Protocol population. Descriptive statistics were presented, and all efficacy measures were summarized and tabulated.

The primary assessments of interest were the ability to increase the TSH level in patients with an inability to elevate endogenous TSH and the avoidance of a pre-specified morbidity during Thyrogen® use that had occurred during prior thyroid hormone withdrawal.

Secondary assessments of interest included the change from baseline in Tg values, symptomatology, and pain medication regimen, and change of scan result as compared to the most recent scan of the same type.

Summary

Thyrogen® was requested for 41 (36%) patients due to their inability to generate $\geq$ 25 mU/L TSH. Thyrogen was requested for 76 (66%) patients to avoid potentially life-threatening conditions. Three patients received Thyrogen® for both reasons. Approximately 52% of patients were female, 48% were male, and 81% were Caucasian. The mean patient age was 59.0 years. The most common types of thyroid cancer were papillary (47%), follicular (28%), and a follicular variant of papillary cancer (14%).

Safety Results:

Thirteen patients died, and 11 patients had non-fatal serious adverse events. Two serious adverse events were considered related to Thyrogen®. A 68 year old woman with follicular cancer metastatic to the spine developed transient worsening of her bone pain three days after Thyrogen® treatment. The second event involved an elderly man with an intact thyroid gland and advance metastatic and local disease. Soon after completing treatment his T4 increased markedly and he developed atrial fibrillation. This was followed by a fatal myocardial infarction.

During the Thyrogen® Compassionate Use Program, fifteen of 115 patients experienced a total of 27 non-serious related adverse events. Only skeletal pain and headache were reported by more than one patient.

Efficacy Results

- Thyrogen® 0.9 mg injections when given intramuscularly as recommended successfully increased serum TSH levels $\geq$ 25 uU/mL in every patient.
- Thyrogen® caused the serum Tg level to increase further in every patient who had a detectable level of Tg in the blood. This implies that Thyrogen® was having a biological effect on thyroid or thyroid cancer tissue in every case in which there were detectable levels of Tg present.
- Thyrogen® allowed radioiodine uptake to occur in thyroid remnant and thyroid cancer tissue in at least 105 out of 115 patients.
- Use of Thyrogen® instead of use of withdrawal of thyroid hormone suppression appeared to prevent the majority of pre-specified complication-types that had actually occurred previously in these patients during withdrawal of thyroid hormone. Use of Thyrogen® also appeared to prevent the majority of pre-specified complication-types that were of concern to these patient's physicians even though these event-types had not actually occurred previously in the patients.
- Use of Thyrogen® plus high-dose radioiodine provided objective clinical benefit in many patients, such as improvement in the global status of symptoms, improvement in specific symptoms (e.g., bone pain), reduction in pain medication use, improvement in scans, and decline in serum Tg levels. Of note, trends in these parameters did not always track together in a given patient. Clinical symptoms and pain medication use may have improved over several months in spite of rising Tg levels, for example. Thus, the objective clinical benefit derived from Thyrogen® and radioiodine treatment in this study is best assessed by a comprehensive clinical review of specific cases.
- Thyrogen® use was associated in some patients with acute worsening of some cancer symptoms, such as bone

pain, that likely was due to an effect of Thyrogen® on the metabolic activity or transient swelling of thyroid cancer tissue. In several patients this acute worsening of symptoms was followed by chronically improved symptoms.

- Many of the patients in this study were very ill; however, 99/115 (86%) patients did not experience a related AE or SAE. Fifteen of 115 (13%) patients experienced a total of 27 non-serious related AEs. Thirteen patients died, and 11 patients had SAEs but did not die during the study. Of these deaths and SAEs, 2 patients had events (atrial fibrillation and fatal myocardial infarction; transient worsening of worsening of metastatic pain) that were considered related to Thyrogen® administration; all other SAEs and deaths were considered unrelated to Thyrogen®.
- Use of Thyrogen® with radioiodine therapy has a favorable risk/benefit profile in this population of differentiated thyroid cancer patients.

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