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NAME OF SPONSOR/COMPANY:

Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142

TITLE OF STUDY:

Protocol THYR-008-00: A Randomized, Controlled, Open-Label, Multi-National Pilot Study of Thyroid Remnant Ablation Comparing the Safety and Ablation Rate Following 131I Administration Using Thyrogen® versus the Safety and Ablation Rate Following 131I Administration in the Hypothyroid State

INVESTIGATORS AND STUDY CENTER(S):

A total of 9 multinational principal investigators located in the US, Europe, and Canada

STUDIED PERIOD:

First Patient Enrolled: 17 December 2001
Last Patient Completed: 26 September 2003

PHASE OF DEVELOPMENT:

Phase 3

OBJECTIVES:

The primary objectives of the study were: 1) to demonstrate that the use of Thyrogen in euthyroid patients (thyroid stimulating hormone [TSH] ≤ 5 mU/L) undergoing radioiodine remnant ablation with 100 mCi (3.7 GBq) ^{131}I results in a comparable ablation rate to patients undergoing radioiodine remnant ablation in the hypothyroid state (TSH ≥ 25 mU/L) with 100 mCi (3.7 GBq) ^{131}I, and 2) to document the safety profile of Thyrogen when used for radioiodine remnant ablation.

The Secondary objectives of the study were: 1) to examine the Quality of Life in patients treated using Thyrogen in comparison to patients treated in the hypothyroid state; and 2) to compare the radioiodine uptake and retention into the thyroid bed, as well as radiation exposure to the remainder of the body, in euthyroid patients using Thyrogen and patients treated in the hypothyroid state.

METHODOLOGY:

Following a total/near-total thyroidectomy, eligible patients provided written informed consent within 14 days post-surgery. Patients were then randomized to 1 of 2 groups: the Euthyroid or the Hypothyroid group.

Once randomized, patients in the Euthyroid group received thyroid hormone suppression therapy (THST) for 4 weeks. At the end of the fourth week, the patient's TSH level was measured. If the TSH level was ≤ 5 mU/L, Thyrogen (0.9 mg) was administered intramuscularly (IM) once daily (qd) for 2 days. Twenty-four hours following the second dose of Thyrogen, an ablative activity of ^{131}I (100 mCi; 3.7 GBq) was administered. All patients then underwent post-treatment whole-body scanning (WBS) and remnant-neck imaging at 48 hours, at 72 to 96 hours, and at 96 to 168 hours (preferably 120 hours) following ablation. In addition, the study allowed for the option to perform scans at 24 hours and between 144 and 168 hours after ablation. Following the final post-treatment scan, patients in the Euthyroid group continued THST.

Patients randomized to the Hypothyroid Group did not receive THST after randomization. These individuals were monitored for at least 4 weeks or until their TSH was ≥ 25 mU/L. Patients were given an ablative dose of ^{131}I (100 mCi, 3.7 GBq). If the patient's TSH was < 25 mU/L at the end of the fourth week, the patient's TSH was measured again 1 week later. Patients then underwent post-treatment WBS and remnant-neck imaging at 48 hours, at 72 to 96 hours, and at 96 to 168 hours (preferably 120 hours) following ablation. In addition, the study allowed for the option to perform scans at 24 hours and between 144 and 168 hours post ablation. Following the final post-treatment scan, patients in the Hypothyroid group commenced THST.

Eight (± l) months later, patients in both the Euthyroid and Hypothyroid groups received Thyrogen (0.9 mg qd for 2 days) followed by an activity of ^{131}I (4 mCi; 0.15 GBq), in preparation for 48-hour WBS and remnant-neck imaging.

Patients with a negative neck scan (i.e., no visible uptake or, if visible uptake, less than 0.1 % uptake in the thyroid bed) 8 (± 1) months following the ^{131}I treatment were considered successfully ablated.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

Approximately 60 patients were planned and a total of 63 patients were analyzed.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Patients who met the following inclusion criteria were eligible to participate in this study (list is not exhaustive):

Patients who were at least 18 years old.

Patients with newly diagnosed differentiated papillary or follicular thyroid carcinoma, including papillary-follicular variant, characterized as “T2, N0 or N1, and M0” or as “T1, N1, and M0”.

Patients with a total or near-total thyroidectomy within 2 weeks prior to enrollment.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Thyrogen (Treatment & Follow-up scan); 0.9 mg intramuscular injection for 2 days.

DURATION OF TREATMENT:

The Treatment Period for each patient lasted approximately 8 months. The study period was defined as the time from randomization to 1 day after the 8 (± 1) month follow-up WBS.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

For the ablative treatment, 100 mCi (3.7 GBq) of ^{131}I was used.

For the follow-up WBS and remnant-neck imaging to determine success or failure, 4 mCi (0.15 GBq) of ^{131}I was used.

CRITERIA FOR EVALUATION:
Criteria For Evaluation - Efficacy:
The primary efficacy variable was successful thyroid remnant ablation, as assessed by the 8 (±1) month follow-up scan. A patient with a negative neck scan (no visible uptake or if visible below 0.1% uptake in the thyroid bed) 8 (±1) months following the ablation treatment were considered a treatment success.

Secondary efficacy variables were individual and mean TSH and thyroglobulin (Tg) levels, and radioiodine kinetics (activity-time curves, half-life [if appropriate], residence time, and area under the activity-time curve). Creatinine clearance rates (mL/min) were evaluated in order to assess patient kidney function and the relationship between the ^{131}I clearance rate and renal function.

Criteria For Evaluation - Safety:
Vital signs, hematologic signs, blood chemistry, AEs, and development of antibodies to Thyrogen were evaluated for safety.

Criteria For Evaluation - Quality Of Life:
Changes in each patient’s quality of life measures were monitored using the SF-36 and Billewicz scales and information recorded in the patient diary.

STATISTICAL METHODS:
The Intent-to-Treat (ITT) population consisted of all patients who signed an informed consent and who were randomized. The Per-Protocol (PP) population consisted of all ITT subjects who satisfied the TSH-level requirements in the study design,

and had no major study protocol violations or deviations (including deviations from the inclusion/exclusion criteria) deemed to have an impact on the primary efficacy assessments.

Statistical Methods - Efficacy:
Descriptive statistics of efficacy variables and 95% confidence intervals (CIs) on the difference between the ablation rates in the 2 treatment groups, with a predefined clinically relevant difference of 20%.

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

Summary - Efficacy Results:
The predefined primary criterion for successful ablation (no visible uptake in the thyroid bed, or if visible, fractional uptake less than 0.1% of administered activity) on neck scans performed 8 months after therapy was satisfied in 100% of patients in both treatment groups. Another criterion for ablation, an rhTSH-stimulated serum Tg less than 2 ng/mL (in patients negative for significant anti-Tg antibody), was fulfilled by 23 of 24 (96%) of patients in the rhTSH-treated (Euthyroid) Group, and was fulfilled by 18 of 21 (86%) of patients in the Hypothyroid Group. Quality of life was well preserved in the Euthyroid Group compared to the Hypothyroid Group, as demonstrated using the Billewicz hypothyroidism scale. The Euthyroid Group had statistically significantly more favorable SF-36 Health Assessment Scale scores in five of eight categories. Euthyroid patients also had a statistically significant one-third lower radiation dose to the blood compared to hypothyroid patients.

Summary - Safety Results:
Treatment with Thyrogen was well-tolerated. There were no deaths reported during the conduct of this study. Two patients experienced a serious adverse event (SAE) before the start of treatment; one patient had finger infection during pretreatment period and another patient developed thrombophlebitis at screening. Three patients experienced 5 SAEs after the start of treatment in the Hypothyroid group; one patient was diagnosed with lung metastasis and another patient experienced myocardial infraction, angina pectoris and coronary artery disease. In the Euthyroid group, one patient developed pancreatitis. None of these SAEs were related to Thyrogen. The frequencies of both SAEs and severe AEs were slightly lower in the Euthyroid group than in the Hypothyroid group (insomnia was reported in 4 patients in the Hypothyroid group and 3 in the Euthyroid group, anxiety was reported in 2 patient in the Euthyroid group and none in the Hypothyroid). The total frequency of AEs was similar in both groups, fatigue was reported in 5 patients in both the hypothyroid and Euthyroid groups, pain was reported in 3 patients in both groups. These findings strongly suggest that the risk of undesirable experiences or health effects is not higher when remnant ablation occurs under Thyrogen stimulation than under stimulation by endogenous TSH, i.e., in the hypothyroid state.

These results also suggest that Thyrogen can be safely administered to stimulate remnant ablation with radioiodine in patients with well-differentiated thyroid cancer.

Based on report prepared on: 02 June 2004
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