

## Protocol TSH94-0301: Pharmacokinetic Assessment of Thyrogen® in Patients with Thyroid Cancer.

*These results are supplied for informational purposes only.  
Prescribing decisions should be made based on the approved package insert in the country of prescription.*

### Investigators and Study Center(s)

This was a multicenter study conducted at 4 sites in the United States.

### Studied Period

First patient enrolled: 13 May 1994  
Last patient completed: 18 September 1994

### Phase of Development

Phase 1

### Objectives

The objectives of this study were:

- To determine the pharmacokinetic profile of Thyrogen®.
- To establish the bioequivalence of the 3.6 mg/mL (Lot A) and 0.9 mg/mL (Lot B) formulations of Thyrogen®.

### Methodology

The study was conducted as a 2-arm (Arm I and Arm II) pharmacokinetic evaluation. Each arm was conducted using a randomized 2-way crossover design. Data from both arms were used to determine the pharmacokinetic profile of Thyrogen®, including absorption, distribution, and elimination. Patients were randomized into either the study of bioequivalence (Arm I) or the study of bioavailability (Arm II). Within each group, patients were further randomized to order of treatment (Lot A/Lot B or intramuscular/intravenous). Arm I was designed to determine the bioequivalence of the intramuscular (IM) administration of a 0.9 mg dose of the 2 formulations of Thyrogen®. Arm II was designed to provide data on the absolute bioavailability of Thyrogen® after IM administration. The first patients randomized to Arms II and intravenous (IV) administration experienced immediate severe nausea, vomiting, and diaphoresis. As a result, Arm II was discontinued before any additional Arm II patients were treated intravenously.

### Number of Patients (Planned and Analyzed)

Twenty patients were enrolled in the study.

### Diagnosis and Main Criteria for Inclusion

- Adult male and female patients with well differentiated thyroid cancer (papillary, follicular, or Hürthle cell) on thyroid hormone replacement therapy.
- Patients had undergone successful near-total thyroidectomy and radioiodine ablation and/or therapy and therefore were at low risk of having metastatic disease, confirmed by a negative radioiodine scan or thyroglobulin (Tg)  $\geq 5$  ng/mL within 1 year to enrollment of the study.
- Patients previously entered in a Thyrogen® study were eligible, since all patients have tested negative for Thyrogen® antibody production.

### Test Product, Dose, and Mode of Administration

Thyrogen®, 2 doses (3.6 mg/mL and 0.9 mg/mL) separated by a 14-day washout period, IM and intravenous (IV)

Arm I was used to determine the pharmacokinetic profile of Thyrogen<sup>®</sup> IM administration.

Arm II was designed to determine the absolute bioavailability of Thyrogen<sup>®</sup>. This was established after comparing both pharmacokinetic data of both IM dose and an IV dose of Thyrogen<sup>®</sup>.

Each arm employed a randomized 2-way crossover design. Each patient received 2 separate single doses of Thyrogen<sup>®</sup>, with each dose separated by a 14-day washout period.

#### **Duration of Treatment**

Two single doses separated by a 14-day washout period.

#### **Reference Therapy, Dose and Mode of Administration**

N/A.

#### **CRITERIA FOR EVALUATION**

##### **Efficacy**

N/A.

##### **Safety**

Vital signs, hematologic signs, blood chemistry, immune response to Thyrogen<sup>®</sup>, and adverse events (AEs) were evaluated for safety.

##### **Pharmacokinetic**

The pharmacokinetic criteria included the maximum concentration, time to peak concentration, elimination half-life, clearance, the area under the time-concentration curve, and the total volume of distribution. Bioequivalence was evaluated based on a comparison of the half-lives, maximum concentrations, and areas under the time-concentration curves of the 2 formulations.

#### **STATISTICAL METHODS**

##### **Efficacy**

N/A.

##### **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.

##### **Pharmacokinetic**

Analysis of variance (ANOVA) was used to compare the mean pharmacokinetic measures associated with the 2 formulations. The null hypothesis was that the 2 formulations were not equivalent for a given parameter. Equivalence for a parameter was defined to occur when the 90% confidence interval for the ratio of the means fell entirely between 80% and 125%.

##### **Summary**

The pharmacokinetic profiles of two Thyrogen<sup>®</sup> formulations have been evaluated including T<sub>max</sub>, (C<sub>max</sub>), log (C<sub>max</sub>), (AUC), log (AUC), CL, V<sub>d</sub>, BETA and T<sub>1/2</sub> after intramuscular administration of a 0.9mg dose.

The bioequivalence of the two formulations, the 3.6 mg/mL and 0.9 mg/mL, was evaluated based on the comparability of T<sub>1/2</sub>, log (C<sub>max</sub>) and log (AUC). The results established that the two formulations of Thyrogen<sup>®</sup> are bioequivalent.

### **Efficacy Results**

N/A.

### **Safety Results**

There were no serious adverse events reported for the study. However, the first study patient to receive a 0.3 mg intravenous (IV) dose of Thyrogen<sup>®</sup> experienced abrupt and severe nausea, vomiting, and diaphoresis 15 minutes post injection. The adverse reaction lasted approximately 30 minutes and the patient fully recovered within 45 minutes. As a result, Arm II of the study (the only arm that included IV Thyrogen<sup>®</sup> administration) was discontinued. Thyrogen<sup>®</sup> was safe and generally well tolerated by patients when delivered by an intramuscular (IM) injection. Transient nausea in 8 patients and headaches in 5 patients were the most frequent Thyrogen<sup>®</sup>-related AEs in this study arm.

### **Pharmacokinetic Results**

ANOVA found no significant differences between formulations in mean maximum concentration, time to peak concentration, clearance, area under the time-concentration curve, and the total volume of distribution. The mean elimination half-life was significantly ( $p < 0.02$ ) longer for the 0.9 mg/mL formulation than for the 3.6 mg/mL formulation. The 90% confidence interval of the ratio of the means of log (maximum concentration) and log (area under the time-concentration curve) ranged from 0.895 to 0.952. These results established that the 2 formulations of Thyrogen<sup>®</sup> are bioequivalent.

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