CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020898

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	**20-898**
Thyrotropin α for Injection (Thyrogen®)	
Submission Date:	**12 December 1997** **30 January 1998** **13 February 1998** **07 April 1998** **07 May 1998**
Type of Submission:	**New Drug Application (1P)**
Reviewer:	**Michael J. Fossler**

Synopsis

Genzyme has submitted NDA 20-898 in support of thyrotropin α (Thyrogen®). Thyrotropin α (also called thyroid stimulating hormone, or TSH) is a recombinant form of human TSH which is naturally produced by the pituitary gland. The proposed indication is for use as an adjunct to radioiodine imaging and/or serum thyroglobulin testing for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy. The recommended dose is 0.9 mg IM every 24 hours for two doses, to be given in the buttocks only. If approved, Thyrogen® will be supplied as a sterile lyophilized product in single-use vials containing 1.1 mg/vial.

Two studies were submitted to support the Clinical Pharmacology portion of the labeling. Protocol TSH91-0601 was a safety and dose-ranging study in 18 patients with thyroid cancer. Protocol TSH91-0301 was a three-way randomized cross-over study designed to determine the absolute bioavailability of Thyrogen after IM injection, as well to determine the bioequivalence of the initial formulation (used in Phase 1-2 as well as in the first Phase 3 trial) and the market formulation, which was used in the second Phase 3 study. No additional studies (such as special populations, metabolism) were submitted.

Little data on the absolute bioavailability of TSH are available. Study TSH94-0301 was originally designed to determine the absolute bioavailability of TSH; however this part of the study was discontinued after the first patient was treated due to protracted nausea and vomiting. No relative bioavailability studies (e.g., subcutaneous vs. intramuscular) have been performed. A bioequivalence study was performed in 24 (16 completed) patients with thyroid cancer given a single dose of TSH (0.9 mg) of either the market or clinical formulations in a randomized crossover design with a 14 day wash-out between treatments. The results indicate that the two formulations are not bioequivalent, with the 90% confidence intervals for Cmax (76.7% - 110%) failing the bioequivalence criterion of 80-125%. No metabolism studies have been performed using thyrotropin α. The organ(s) of endogenous TSH clearance in man have not been identified, but studies of pituitary-derived TSH suggest the involvement of the liver and kidneys.

Due to the risk of TSH-induced hyperthyroidism, both pharmacokinetics studies were performed in patients. Study TSH91-0601 was a dose-ranging study performed to determine the optimum dosage regimen for Thyrogen® . Blood samples for pharmacokinetic evaluation of exogenous TSH were taken over 24-96 hours, depending on the dosing regimen. Full TSH profiles were only obtained for the last dose in each regimen. In addition, the sampling for each regimen is not long enough to adequately characterize the terminal phase, so the data are of limited usefulness, other than to demonstrate that TSH levels > 25 μU/ml are achieved with each regimen. The single-dose bioequivalence study showed that peak concentrations of 62-202 mU/ml are reached 3-24 hours after a

single IM injection. The apparent elimination half-life ranges between 11.5 - 46 hours. This is probably due t slow, sustained absorption from the injection site, as data from a single patient given an IV injection of Thyrogen® indicate that the half-life of TSH may be around 8 hours.

No dose linearity studies were performed. In the initial dose-ranging study, the trough (Cmin) values of TSH taken 24 hours after the first dose indicate that there may be a disproportionate increase in TSH AUC above a dose of 1.8 mg, although there are too few patients in the study to be conclusive.

A small dose-ranging PK/PD study was performed in 19 thyroid cancer patients who had undergone thyroidectomy and were scheduled to receive a ^{131}I whole body scan to determine the extent of residual tissue and to identify any disease outside the thyroid bed. Patients were randomized into one of the following dosing regimens:

1) 10 units x 1 dose (n=3)
2) 10 units q 24 hrs x 2 doses (n=3)
3) 10 units q 24 hrs x 3 (n=3)
4) 20 units x 1 dose (n=3)
5) 20 units q 24 hrs x 2 doses (n=3)
6) 30 units x 1 dose (n=3)

Pharmacodynamic data related to the efficacy of TSH collected during the study include percent ^{131}I uptake for Thyrogen® and withdrawal scans, serum thyroglobulin (Tg) response and rating of the quality of the scans by an independent reviewer.

The results show that the uptake of ^{131}I (which is a measure of thyroid tissue activation) is higher in 12/18 (67%) patients in the study after the withdrawal phase, 5/18 (28%) after administration of TSH, and about the same in 1 patient. These data suggest that withdrawal is superior to treatment with Thyrogen® in stimulation of residual thyroid tissue and/or cancer; however, these data must be interpreted with considerable caution since ^{131}I clearance is about 40-50% lower in hypothyroid patients as compared with euthyroid patients. Since the same scanning dose of ^{131}I was administered after both treatments (withdrawal and TSH), this means that the subjects may have received twice the effective dose of ^{131}I during the withdrawal period. It is important to note that the same practice was followed in the Phase 3 trials. Moreover, despite the firm having this information, no investigations examining the optimum scanning dose of ^{131}I in Thyrogen® -treated patients have been performed by the firm.

Looking at the serum Tg results, although it appears as though thyrotropin has a stimulatory effect on thyroid tissue (10/14 evaluable subjects had Tg levels on TSH increase from baseline), it is equally clear that the stimulatory effect of thyrotropin is inferior to withdrawal at the doses studied, as 11/14 evaluable subjects (nearly 80%) had higher Tg levels (in many cases, much higher) after withdrawal therapy. These data strongly suggest that the optimum dosing regimen of Thyrogen® has not yet been determined.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 20-898, and recommends non-approval of this application due to

If the Division of Metabolic and Endocrine Drug Products feels that this drug should be approved, the **Labeling Comments** should be sent to the firm, and the text under **Comments to firm** forwarded to the firm as Phase 4 commitments. If this NDA is not approved by HFD-510, the text under **Comments to firm** should be forwarded to the firm as studies which should be performed prior to the initiation of additional Phase 3 trials.

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Appendix of Study Summaries (available from DPE-2 upon request)

Abbreviations used in text

TSH - thyroid stimulating hormone, also known as thyrotropin
Tg - thyroglobulin
T4 - levothyroxine
T3 - triiodothyronine

1 unit of thyrotropin = 0.09 mg

I. Background

Genzyme has submitted NDA 20-898 in support of thyrotropin α (Thyrogen®). Thyrotropin α (also called thyroid stimulating hormone, or TSH) is a recombinant form of human TSH which is naturally produced by the pituitary gland. The proposed indication is for use as an adjunct to radioiodine imaging and/or serum thyroglobulin testing for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy.

Thyrotropin α is a heterodimeric glycoprotein consisting of two subunits linked non-covalently. The α subunit contains 92 amino acids, and the β unit contains 118 amino acids. The overall molecular formula of Thyrogen® is $C_{1039}H_{1602}N_{274}O_{307}S_{27}$. The molecular weight of Thyrogen® is 23.7 kD.

A brief review of the current therapy for thyroid cancer will be useful in evaluating the clinical pharmacology data presented in the application. Once thyroid cancer is diagnosed, a total or near-total thyroidectomy is usually performed. No thyroid hormone replacement is given, and the TSH is monitored, with the goal being a rise in TSH to at least 30 μU/ml, to allow for sufficient stimulation of iodine uptake. Five to six weeks after surgery, the patient is given a scanning dose (2-4 mCi) of radioiodine (^{131}I) and undergoes whole body scanning with a gamma camera. Areas of well-differentiated cancer or thyroid remnants will take up the ^{131}I and will be visualized. Then radioablative doses (30-150 mCi) may be administered to destroy the remnant tissue and cancer. Once ablation is completed, the patient is started on thyroid hormone (levothyroxine or triiodothyronine), with the treatment goal generally being a serum TSH < 0.5 μU/ml. This is generally referred to as thyroid hormone suppression therapy (THST).

Patients must be monitored at regular intervals for the remainder of their lives for the recurrence of cancer. Serum thyroglobulin (Tg) is a sensitive marker of tumor recurrence in patients who have undergone complete ablation. Since Tg levels should be zero in a patient that has been successfully ablated, a detectable serum Tg indicates the recurrence of cancer. Unfortunately, Tg levels are often suppressed by hormone replacement therapy, so periodic whole body scanning is still needed. Typically this is done by stopping the patient's thyroid hormone for 4-6 weeks (2 weeks if triiodothyronine is used), and monitoring serum TSH, until it reaches 30 μU/ml. Then the patient is given a scanning dose of ^{131}I and scanned as previously described. Serum Tg is also measured. The decision to treat the patient with further ablation therapy depends on the results of the whole body scan and the serum Tg level achieved after withdrawal of thyroid hormone[1].

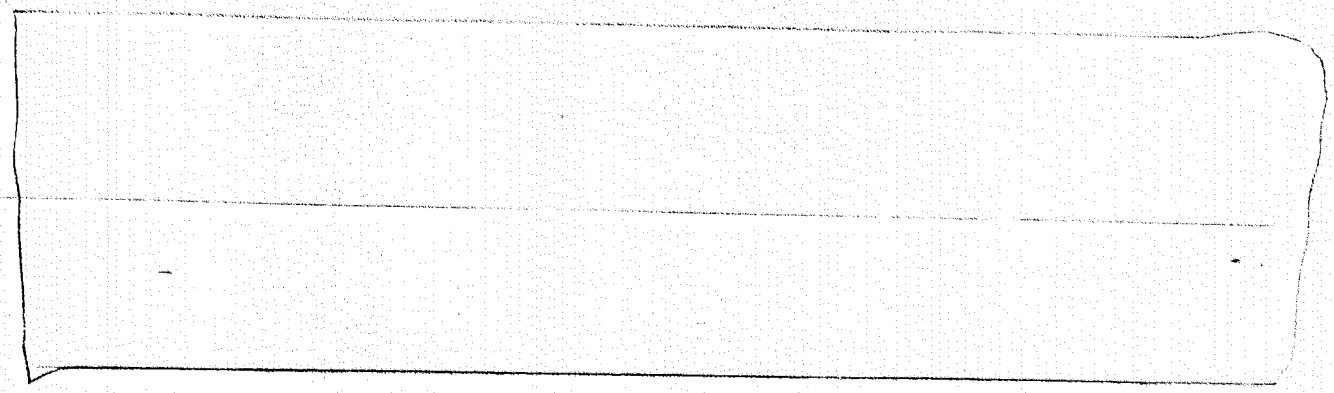
Unfortunately, withdrawal therapy has one severe drawback: patients must become hypothyroid periodically and experience the weight gain, myxedema, alopecia and mental depression that goes along with that state. The administration of exogenous TSH may allow patients to remain euthyroid, while still stimulating cancer tissue to produce Tg and take up ^{131}I.

II. Assay Method and Validation

[redacted]

[1] Feld S. AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma

[2] These values were not supplied to the reviewer, despite repeated requests for all assay validation data.



III. Bioavailability and Bioequivalence

Absolute and Relative Bioavailability

Little data on the absolute bioavailability of TSH are available. StudyTSH94-0301 was originally designed to determine the absolute bioavailability of TSH; however this part of the study was discontinued after the first patient was treated due to protracted nausea and vomiting. The data from this single patient suggest that the absolute bioavailability may be around 80%.

No relative bioavailability studies (e.g., subcutaneous vs. intramuscular) have been performed.

Bioequivalence

The market formulation of TSH contains 0.9 mg of drug, whereas the formulation used in the clinical trials contained 3.6 mg. The difference is due merely to fill weight, as the amount and type of excipients used is exactly the same in the two formulations. However, the concentration after reconstitution was much more concentrated in the clinical formulation (3.6 mg/ml) than that in the market formulation (0.9 mg/ml), which could affect the rate and/or extent of absorption. The market formulation was also used in the second Phase 3 trial. A bioequivalence study was performed in 24 (16 completed) patients with thyroid cancer given a single dose of TSH (0.9 mg) in a randomized crossover design with a 14 day wash-out between treatments. The results are shown in Table 2.

Table 2: Results of TSH94-0301 bioequivalence study.

Parameter	Mean Ratio[‡] (market/clinical) (90% CI)
AUC(0-last)	105 (93.6 - 117)
AUC(0-inf.)	113 (102 - 126)
Cmax	91.9 (76.7 - 110)

[‡]back-transformed from the natural log

Using AUC(0-last), the two formulations appear to be equivalent in extent of absorption. However, using AUC(0-inf.), the market formulation appears to be just slightly more bioavailable than the clinical formulation. This may be due to the fact that in six subjects, the AUC(0-last) did not account for at least 80% of the AUC(0-inf.) after treatment with the market formulation. Since for this treatment, a large portion of the AUC(0-inf.) is extrapolated, the AUC(0-inf.) values may be less reliable. This difference between the two treatments suggests that the market formulation is absorbed more slowly than the clinical formulation, which is also borne out by the confidence intervals for Cmax. Overall, the results indicate that the proposed market formulation is equally bioavailable to the clinical formulation, but is absorbed somewhat more slowly. It is unclear whether this is a clinically significant difference.

IV. Metabolism

No studies have been performed. The organ(s) of TSH clearance in man have not been identified, but studies of pituitary-derived TSH suggest the involvement of the liver and kidneys.

V. Pharmacokinetics

Normal Volunteers

No studies were performed in normal volunteers due to the risk of TSH-induced hyperthyroidism.

Patients

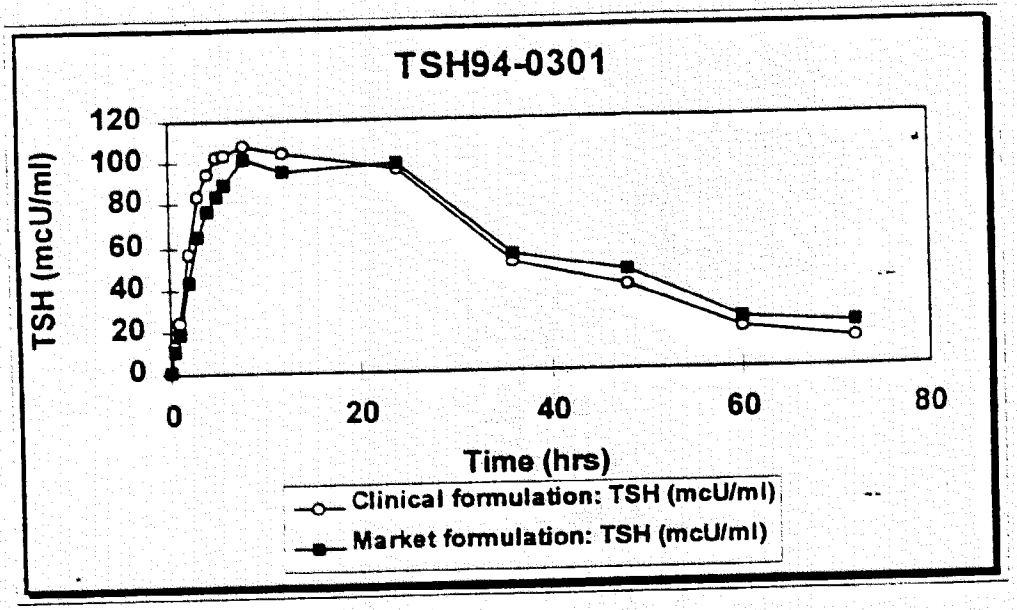
Both studies submitted to the NDA enrolled patients with thyroid cancer. Study TSH94-0301 was a single dose bioequivalence/absolute bioavailability study. Patients were randomized to one of two arms: 1) single-dose randomized crossover study comparing the clinical and market formulations of Thyrogen® , 2) single dose randomized crossover study comparing the bioavailability of an intramuscular injection of Thyrogen® to an intravenous bolus dose. Arm 2 of the study was discontinued after only one patient was enrolled, due to severe nausea and vomiting immediately after an iv injection of TSH. A summary of the pharmacokinetics of TSH from both arms of the study is shown below. Figure 1 shows a plot of the mean TSH curves resulting from the study.

Table 2: Single-dose pharmacokinetics of TSH after intramuscular injection of 0.9 mg Thyrogen® in 16 patients with thyroid cancer

Formulation	AUC(0-∞) (μU*hr/ml)	AUC(0-72) (μU*hr/ml)	Cmax (μU/ml)	tmax‡ (hrs)	t½ (hrs)
Clinical	4642±1617	4244±1475	130±45	8 (3 -24)	19±5
Market	5167±1702	4314±1275	116±38	10 (2 - 24)	25 ± 10

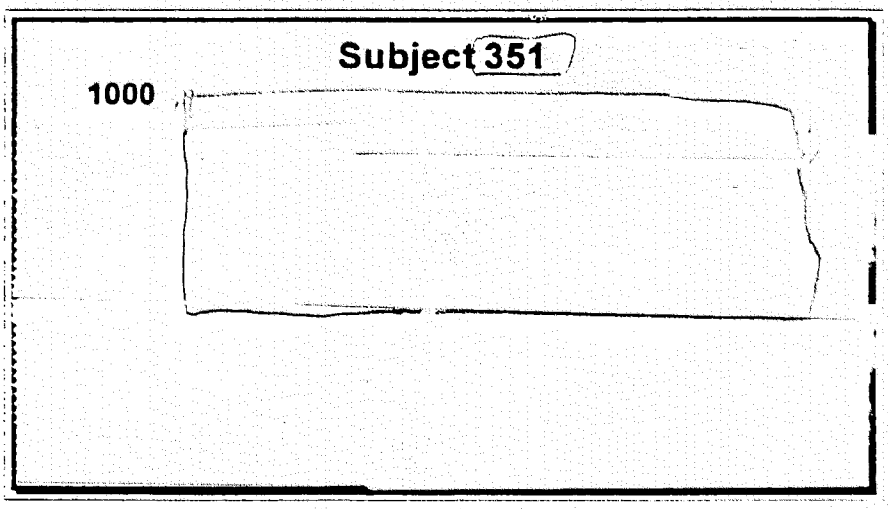
‡ median (min - max)

Figure 1: Mean TSH curves from Study TSH94-0301.



Based on the above data, it appears that Thyrogen® is absorbed slowly from the IM injection (tmax 2 - 24 hours), with the market formulation absorbed a bit more slowly than the clinical trials formulation. These data suggest that ka < kel, and that the apparent t½ obtained in this study may be due to both absorption and elimination. That this is probably occurring is suggested by the data from the single patient given TSH intravenously (Figure 2). The t½ of TSH in this patient is 7.7 hours, which is considerably shorter than any single estimate derived from intramuscular data.

Figure 2: Patient 351, given a single 0.3 mg intravenous bolus of Thyrotropin.



Study TSH91-0601 was a dose-ranging study performed to determine the optimum dosage regimen for Thyrogen® . Blood samples for pharmacokinetic evaluation of exogenous TSH were taken over 24-96 hours, depending on the dosing regimen. Full TSH profiles were only obtained for the last dose in each regimen. In addition, the sampling for each regimen is not long enough to adequately characterize the terminal phase, so the data are of limited usefulness, other than to demonstrate that TSH levels > 25 μU/ml are achieved with each regimen. The data are plotted in Figure 3a-c.

Dose Linearity

No specific studies were performed. In the initial dose-ranging study, the data indicate that there may be a disproportionate increase in TSH AUC above 20 U (Figure 3a), although there are too few patients in the study to be conclusive. Since the maximum dose of Thyrogen® is 10 U (0.9 mg) q 24 hours for 2 doses, this non-linearity is not of much concern.

VI. Special Populations

No studies were performed.

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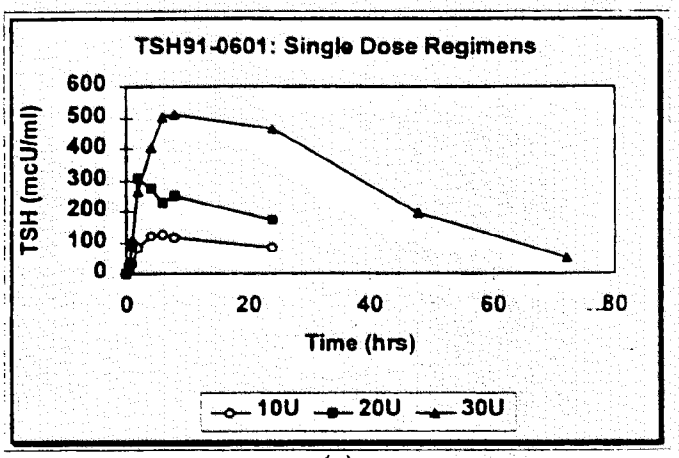
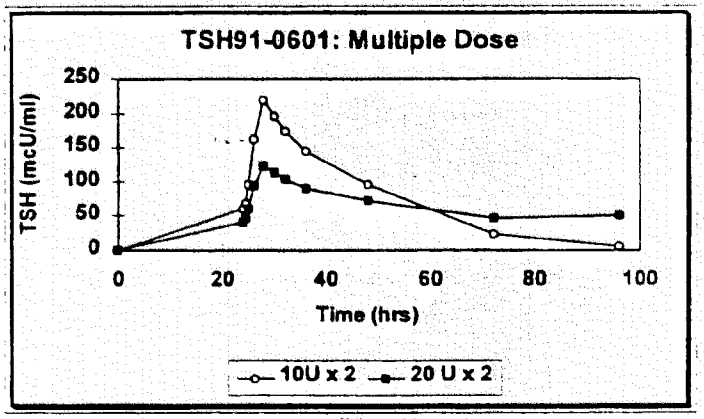
VII. Drug Interactions

No studies were performed.

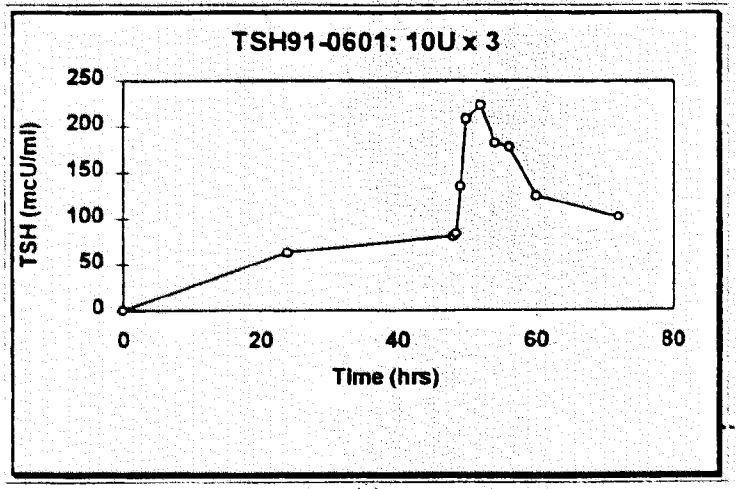
Figure 3: Mean plots of TSH after single and multiple-dose adminstration in thyroid cancer patients. a) 10, 20, or 30 units as a single dose, b) 10 or 20 units given every 24 hours for 2 doses, c) 10 units given every 24 hours for three doses.



(a)



(b)



(c)

VIII. Pharmacokinetic/Pharmacodynamic Relationships

A small dose-ranging PK/PD study was performed in 19 thyroid cancer patients who had undergone thyroidectomy and were scheduled to receive a ^{131}I whole body scan to determine the extent of residual tissue and to identify any disease outside the thyroid bed. Patients were randomized into one of the following dosing regimens:

1) 10 units (0.9 mg) x 1 dose (n=3)
2) 10 units (0.9 mg) q 24 hrs x 2 doses (n=3)
3) 10 units (0.9 mg) q 24 hrs x 3 (n=3)
4) 20 units (1.8 mg) x 1 dose (n=3)
5) 20 units (1.8 mg) q 24 hrs x 2 doses (n=3)
6) 30 units (2.7 mg) x 1 dose (n=3)

Once enrolled, subjects were placed on T3 suppressive therapy until their endogenous TSH levels were suppressed (≤ 0.5 mU/ml). They were then treated with one of the doses of Thyrogen® listed above. Twenty-four hours after the last dose of Thyrogen® , each patient was given a scanning dose (2 mCi) of ^{131}I . After 48 hours, anterior whole body scans were performed using a gamma camera. Each subject was then withdrawn from T3 therapy until adequate endogenous TSH levels (set at ≥25 μU/ml) were achieved, at which point the same scanning dose of ^{131}I was given, and the subjects re-scanned after 48 hours.

The pharmacokinetic results of this study have been previously discussed (See Figure 3a-c, above). Pharmacodynamic data related to the efficacy of TSH collected during the study include percent ^{131}I uptake for Thyrogen® and withdrawal scans, thyroglobulin response (as measured by serum thyroglobulin), and rating of the quality of the scans by an independent reviewer. Because ^{131}I uptake and thyroglobulin response are sensitive measures of thyroid tissue stimulation, the focus will be on these variables as they relate to the selection of a proper dosing regimen.

Table 3 depicts the percent difference in ^{131}I uptake as measured from the cervical region between the two treatments. Uptake of ^{131}I (which is a measure of thyroid tissue activation) is higher in 12/18 (67%) patients in the study after the withdrawal phase, 5/18 (28%) after administration of TSH, and about the same in 1 patient. These data suggest that withdrawal therapy is superior to treatment with Thyrogen® in stimulation of residual thyroid tissue and/or cancer; however, these data must be interpreted with considerable caution since ^{131}I clearance is about 40-50% lower in hypothyroid patients as compared with euthyroid patients. Since the same scanning dose of ^{131}I was administered after both treatments (withdrawal and TSH), ***this means that the subjects may have received twice the effective dose of ^{131}I during the withdrawal period. This introduces a bias in favor of withdrawal. It is important to note that the same practice was followed in the Phase 3 trials. Moreover, despite the firm having this information, no investigations examining the optimum scanning dose of ^{131}I in Thyrogen® -treated patients have been performed by the firm.***

Table 3: Percent difference in ^{131}I uptake in the cervical region after treatment with both Thyrogen® and withdrawal therapy in 18 patients with thyroid cancer. Each number in the table is from an individual patient.

Dosing Regimen (n=3 for all)	Individual % difference in ^{131}I uptake‡ (+ Thyrogen® better, - Withdrawal better)
10U x 1 dose	0, -22%, -127%
20 U x 1 dose	79%, -16%, -44%
30U x 1 dose	-96%, -262%, -333%
10 U x 2 doses	40%, 9%, -74%
20 U x 2 doses	-74%, -127%, -371%
10 U x 3 doses	-226%, 11%, 93.5%

‡Calculated by substracting the withdrawal uptake from the TSH uptake and dividing by the TSH uptake.

Serum thyroglobulin is a very sensitive measure of thyroid tissue stimulation, as well as a good measure of tumor burden. According to the protocol, serum Tg was to be drawn at baseline (pre-treatment), prior to each TSH injection, prior to the administration of ^{131}I and at follow-up. For reasons that are unclear, no samples were taken at the time of the scan for either of the two treatments. Table 4 compares the baseline Tg levels, and those attained at the time of ^{131}I administration for the two treatment arms (thyrotropin or withdrawal). Although it appears as though thyrotropin has a stimulatory effect on thyroid tissue (10/14 evaluable subjects had Tg increase from baseline), it is equally clear that the stimulatory effects of thyrotropin are inferior to withdrawal at the doses studied, as 11/14 evaluable subjects (nearly 80%) had higher Tg levels (in many cases, much higher) after withdrawal therapy. ***These data, scant as they are, strongly suggest that the optimum dosing regimen of Thyrogen® has not yet been determined, and that the dose ultimately chosen for Phase 3 could be expected to be inferior to withdrawal therapy.*** In fact in both Phase 3 studies, Thyrogen® was found to be an erratic stimulator of Tg secretion at the doses studied. The medical officer, in her review states that due to this erratic stimulation of Tg secretion "...not only can we not interpret the clinical significance of a given Thyrogen® Tg level, we can not use it as a reliable surrogate marker for cancer...". That the firm chose not to use these Phase 2 data to design additional studies aimed at optimizing the clinical dose of Thyrogen® is unfortunate.

In fact, data in the literature from as far back as 1983[3] suggest that a 3 day course of bovine TSH did not lead to maximal ^{131}I uptake as compared with withdrawal therapy. More interestingly, data from the same paper which examined the time-course of endogenousTSH, serum Tg, and % ^{131}I uptake, in two thyroid cancer patients undergoing withdrawal, suggest that serum Tg takes about 15 days at TSH levels > 30 μU/ml to reach a maximum (Figure 4).

In a letter to the firm dated 6/23/95, HFD-510 suggested that the firm perform additional Phase 2 studies designed to determine the optimum dose/duration of Thyrogen® . The firm chose not to perform the indicated studies.

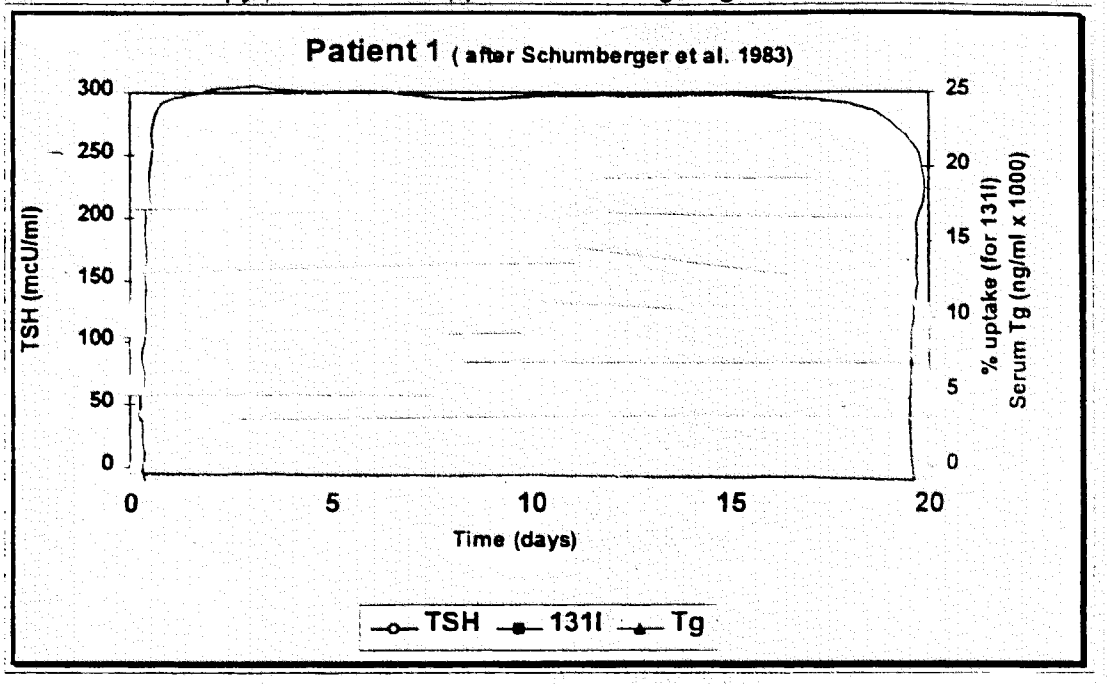
Table 4: Individual Serum Tg values resulting after treatment with either Thyrogen (at the doses indicated) and after withdrawal therapy. N.B. - 0.9 mg is equivalent to 10 units

Dose Group	10 U x 1			20 U x 1			30 U x 1		
Patient #	501	502	503	401	402	403	302	303	504
Baseline Tg									
Thyrogen® Tg									
Withdrawal Tg									
Follow-up									

Dose Group	10 U x 2			20 U x 2			10 U x 3		
Patient #	102	307	505	304	305	306	301	201	202
Baseline Tg									
Thyrogen® Tg									
Withdrawal Tg									
Follow-up									

[3] Schlumberger et al. J. Clin Endo. Metab. (1983) 57:148.

Figure 4: Time-course of serum TSH, Tg, and % ^{131}I uptake in a patient undergoing withdrawal of thyroid hormone therapy (in this case T3) prior to scanning. Figure re-created from Ref. 1.



IX. Dosage and Administration

The dose as recommended in the package insert is 10 units (0.9 mg) given by intramuscular injection in the buttocks every 24 hours for 2 doses. The labeling states that radioiodine should be given 24 hours after the last injection of Thyrogen® ,with the scan performed 48-72 hours after dosing with radioiodine.

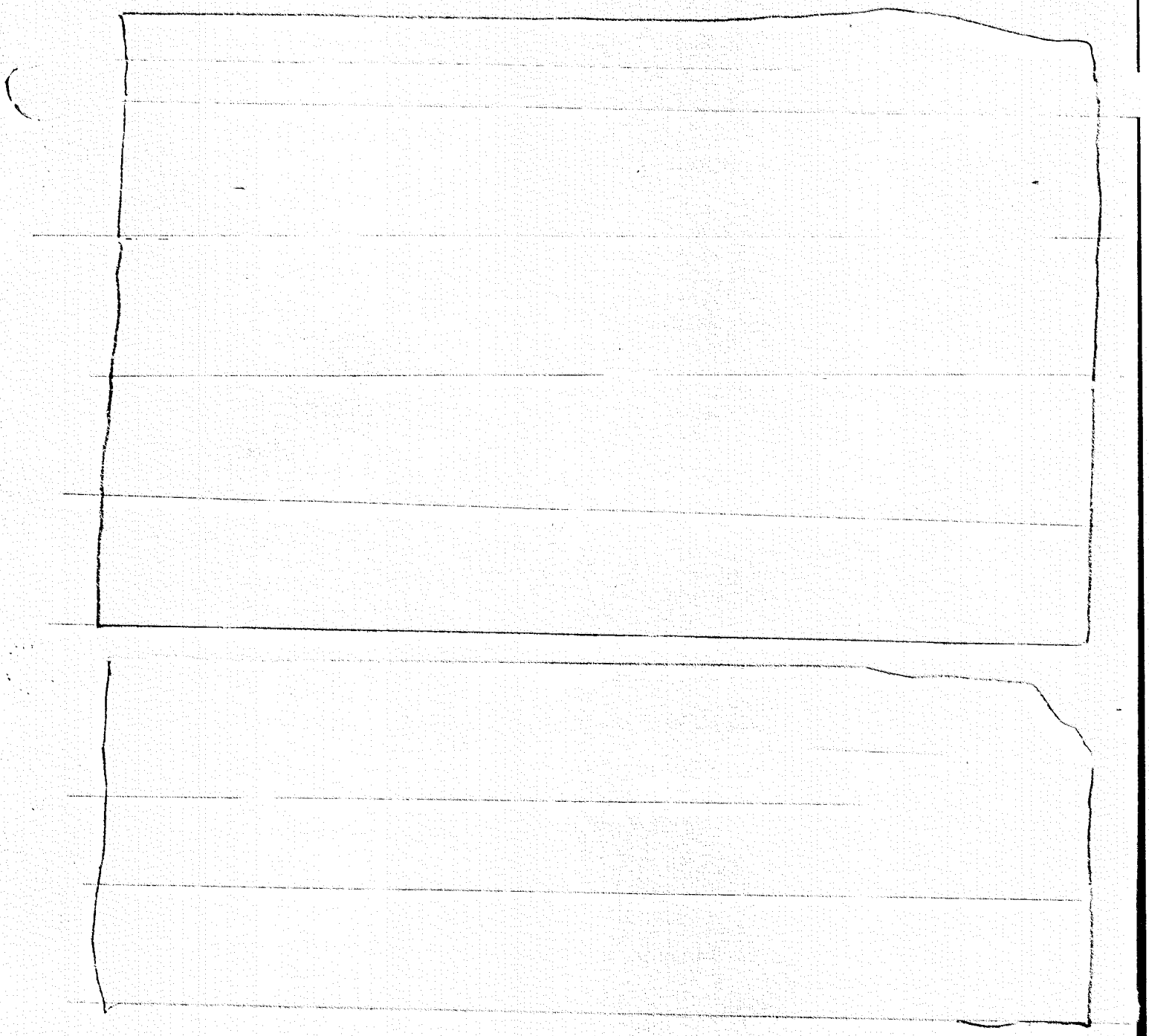
X. Formulation

Thyrogen® is proposed for marketing as single-use lyophilized vials containing 1.1 mg thyrotropin. The specific formulation is listed in Table 5 below.

Table 5: Composition of proposed market formulation of Thyrogen® .

Ingredient	[redacted]
Thyrotropin α	
Mannitol	
Sodium Phosphate	
NaCl	

‡overage is to allow accurate withdrawal of dose from the vial.



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XIII. **Labeling Comments (if drug is approved for marketing)**

1)The text under **Pharmacokinetics** should be replaced with the following:

DRAFT LABELING

XIV. **Signatures**

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/S/ 5/28/98

Michael J. Fossler, Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 5/28/98

version: Final

Office Briefing held 5/14/98 at 10:00 am. Present: Huang, Balian, Mehta, Lesko, Cronenberger, Chen, Selen, Hunt, Wei, Ahn, Fossler

CC: NDA 20-898 (orig., 1 copy), HFD-510(Temeck, Orloff, McCort), HFD-850(Lesko), HFD-870(M. Chen, Fossler, Ahn), HFD-340(Vish), Central Document Room (Barbara Murphy)
Recomendation Code: NA
2/27/98

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