CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020898

MEDICAL REVIEW(S)

NDA 20898
Drug: Thyrogen (recombinant human TSH)
Sponsor: Genzyme

Date submitted: 12/15/97
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Drug: Thyrogen (recombinant human TSH)

[redacted]

Sponsor's [redacted] indication: "Thyrogen is indicated 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."

Proposed dose: 0.9 mg IM q 24 h x 2 doses

Protocol TSH91-0601, a dose-ranging study, and TSH94-0301, a Thyrogen PK study, were phase I/II studies. Efficacy will be discussed briefly here because that will be addressed in detail by Dr. Fossler, Biopharmaceutics Reviewer. Safety will be the primary focus of these two studies in this review.

Protocol TSH91-0601:

This study was designed to study the safety and preliminary efficacy of different Thyrogen dosing regimens. 19 adults (13 F, 6M) with well-differentiated thyroid cancer (16 papillary, 2 follicular and 1 papillary/follicular) were studied.

7 different dosing regimens were studied- all were administered IM and qd:

0.9 mg x 1 day, x 2 days, x 3 days
1.8 mg x 1 day, x 2 days
2.7 mg x 1 day
3.6 mg x 1 day

3 patients were studied at each dosing regimen except for the 3.6 mg dose which was discontinued after enrollment of the first patient due to the occurrence of flushing, vomiting and nausea after Thyrogen administration.

18 patients underwent a near total and 1 patient, a subtotal thyroidectomy. After thyroidectomy, patients were treated with T_3 for a median of 37 days to suppress TSH to $\leq$0.5 mU/L. 24h after Thyrogen, patients received 1-2 mCi ^{131}I; 48h after Thyrogen, a whole body scan (WBS) was conducted and thyroid bed uptake measured. Tg was measured 24 hrs. after the final Thyrogen injection in 10 patients and at 24, 48 and 72 hrs. in 9 patients. After the Thyrogen scan, patients were withdrawn from T_3 to allow TSH levels to increase to $\geq$25 mU/L. Then, Tg was measured and 1-2 mCi ^{131}I was administered. 48 hrs. later, a WBS was performed and ^{131}I uptake was measured. Scan pairs were reviewed by an independent reviewer (IR) who was blinded as to which was the Thyrogen scan and which, the WD scan.

Results:

The following table illustrates the IR rating of the scans:

Dosing Regimen	Thyrogen scan better	Both scans similar	WD scan better
0.9 mg x 1 day	3	0	0
0.9 mg x 2days	0	3	0
0.9 mg x 3days	1	1	1
1.8 mg x 1day	0	3	0
1.8 mg x 2days	0	2	1
2.7 mg x 1 day	0	3	0
3.6 mg x 1 day	0	0	1
Total	4	12	3

Based on the above results, the sponsor concluded that the most promising Thyrogen dosing regimens were 0.9 mg as a single dose, 0.9 mg qd x 2 doses or a single 1.8 mg dose.

48h ^{131}I thyroid bed uptake was higher in 13/19 patients during the WD phase, higher in 4 during the Thyrogen phase and equivalent during both phases in 1 patient. In 1 patient, the comparison of uptake between the Thyrogen and WD phases was confounded by a high amount of residual uptake at the time of the WD scan.

48h thyroid bed uptake and ^{131}I whole body retention were measured in 7 patients. Thyroid bed uptake was higher after WD in 6/7 patients and whole body retention was 2 fold higher during WD (16.8$\pm$7.4%) than after Thyrogen (7.4$\pm$5.0%). These results are expected due to the decreased renal clearance of ^{131}I when patients are hypothyroid. When the thyroid bed uptake was normalized for whole body retention, the difference in uptake

disappeared.

In 17/19 patients, the WD Tg was > Thyrogen Tg and was equivalent in 2 patients. There appeared to be no correlation between Thyrogen Tg and WD Tg.

3/19 (16%) patients experienced adverse events in this study:

1 patient experienced nausea at the 2.7 mg dose;

1 patient experienced nausea, weakness, dizziness and headaches after the 2.7 mg dose

1 patient experienced nausea, vomiting and hot flashes for 8 hrs. after the 3.6 mg dose.

Protocol TSH94-0301:

The primary objectives of this study were to determine the PK profile and to establish the bioequivalence of 2 different formulations of Thyrogen (3.6 mg/ml which had been used in the TSH91-0601 study and 0.9 mg/ml which was projected for use in the first phase III study, TSH92-0601). In addition, this study was designed to determine the absolute bioavailability of Thyrogen after IM and after IV administration. This study, which enrolled 20 patients with well-differentiated thyroid cancer, will be discussed by the biopharmaceutics reviewer, Dr. Fossler. Suffice it to say here, the absolute bioavailability arm of this study was discontinued when, 15 minutes following a 0.3 mg IV bolus of Thyrogen, the first patient experienced severe nausea, vomiting, diaphoresis, hypotension (BP decreased from 115/66 to 81/44) and tachycardia (pulse increased from 75 to 117 bpm), attributed by the investigator to Thyrogen.

For an assessment of the results of the bioequivalence of the 2 formulations, please refer to Dr. Fossler's Biopharmaceutics review.

Safety:

4 patients failed to complete the study. This included the patient described above who experienced nausea, vomiting. diaphoresis, hypotension and tachycardia. Another patient withdrew due to severe nausea, dizziness and headache following Thyrogen administration. Of the remaining 2 patients, one withdrew for treatment of pre-study anemia, and the other, because the absolute bioavailability arm of the study had been discontinued.

A total of 8 patients experienced adverse events in this study. The most commonly reported adverse events related to Thyrogen were nausea, headache, sweating and dizziness.

Protocol TSH92-0601:

STUDY OBJECTIVE:

To determine the safety and effectiveness of Thyrogen when used as an adjunct in the detection of remnants and

cancer in patients with thyroid cancer who have tissue capable of radioiodine uptake.

STUDY DESIGN:

This was a multi center (11 sites), open-label, single arm study. The dosing regimen used was 0.9 mg Thyrogen IM daily for 2 consecutive days. This dosing regimen was chosen for several reasons:

1. There were no reported adverse events with this dosing regimen.
2. Transient nausea was reported in patients rx'd with Thyrogen doses of 1.8 mg and higher.
3. This regimen resulted in sufficient elevation of TSH (>25 mU/L, the level chosen in this study as sufficient for the conduct of radioiodine scanning) for 3-4 days following the first Thyrogen injection.
4. This regimen produced scans which showed all foci of radioiodine uptake indicative of remnant and cancer which were seen on the subsequent withdrawal (WD) scans (see results from TSH91-0601).
5. There was equivalent or higher % radioiodine uptake quantified at the time of the Thyrogen scan compared to the time of the WD scan.

The patient population consisted of adults (≥18 yrs.), of either gender, with well-differentiated thyroid cancer (papillary, follicular or Hurthle cell) scheduled for radioiodine scanning. This included patients undergoing a pre-ablation whole body scan (WBS) shortly after thyroidectomy and follow-up patients returning for a post-ablation WBS.

The main exclusion criteria were:

1. Patients with undifferentiated thyroid cancer.
2. Patients taking drugs known to affect thyroid function.
3. Patients who had previously received bovine TSH.
4. Patients who had IV or IT iodinated contrast material within 3 weeks of study entry.

PROTOCOL SCHEDULE:

Prior to study initiation, pre-ablation patients were placed on THST (thyroid hormone suppressive therapy) sufficient to suppress TSH levels to <0.5 mU/L for a minimum of 4 weeks prior to being treated with Thyrogen. Post-ablation patients continued on a dose of THST sufficient to suppress TSH levels to <0.5 mU/L.

Prior to Thyrogen administration, blood was obtained for measurement of TFTs (TSH, Tg, T4, FT4, T3, thyroid microsomal antibodies and Tg antibodies), chemistries (including creatinine, cholesterol and triglycerides) and urine was obtained

for urinary iodine and creatinine. A hypothyroid symptom assessment was also made at this time (using Billewicz Scale which is an observer-rated evaluation of 14 signs/symptoms of hypothyroidism and the short-form POMS: Profile of Mood States which is a self-administered assessment of 6 mood states: tension-anxiety, depression-dejection, anger-hostility, confusion-bewilderment, vigor-activity and fatigue-inertia).

Each patient then received Thyrogen 0.9 mg IM for two consecutive days while continuing their THST. 24 hrs. after the second injection, blood and urine specimens were obtained (for measurement of the same parameters as at baseline) and each patient received a 2-4 mCi scanning dose of ^{131}I. 48 hrs. after the scanning dose, the patient returned for a Thyrogen WBS and repeat hypothyroid symptom assessment.

The patient then continued on THST for at least 2 weeks to allow TSH levels to return to baseline. The patient was then withdrawn from THST for a minimum of 2 weeks to allow TSH levels to rise to $\geq$ 25 mU/L. When this occurred, blood and urine specimens were again obtained (for measurement of the same parameters as at baseline) and residual radioactivity from the Thyrogen scan was measured in patients who had quantifiable uptake. The patient was then given the same ^{131}I tracer dose ($\pm$ 20%) as previously administered. 48 hrs. after the tracer dose, the withdrawal (WD) scan was performed and the hypothyroid symptom assessment was made. The decision to treat or ablate the patient was based on the results of the WD scan. 1 week later, serum was obtained for measurement of Thyrogen antibodies. (note: this assay used an qualified [redacted] by Genzyme's Immunology Dept.).

EVALUATION OF THE SCANS:

The WBS were reviewed by 3 independent reviewers (IRS) who were not involved in treating the patients. They were blinded as to the identity of the patient, location or the sequence of the scans. The reviewer first rated the technical quality of each film and identified sites of physiological uptake and potential artifacts. Each scan was then rated using the following staging system:

- stage 0: no evidence of uptake
- stage 1: remnants/cancer within the thyroid bed
  - 1A: remnant tissue
  - 1B: thyroglossal duct/pyramidal lobe remnant
- stage 2: uptake within the neck (local or nodal metastases)
- stage 3: distant metastases: mediastinum and/or lungs
  - 3A: diffuse pulmonary disease
  - 3B: nodular pulmonary disease
  - 3C: nodular disease in the mediastinum
- stage 4: distant metastases: bone, brain, liver

4A: bone metastases
4B: brain metastases
4C: liver metastases
4D: other

The reviewers also evaluated each scan for the number and distribution of the lesions.

The reviewers then compared the scan pair for a given patient to determine if the same number and distribution of the lesions was present on both. If yes, the scans were rated as concordant. If not, they were rated as discordant, with the WBS demonstrating a greater number and/or more widespread disease, being designated as the superior scan.

If a consensus had not been reached (2/3 IRS agreed on the reading of a scan pair as concordant or discordant), then, they met as a panel and used extra views, post-therapy scans, etc. to hopefully reach a consensus.

Only those scan pairs in which the IRS had reached a consensus were used in the efficacy analyses.

Evaluation of % Radioiodine Uptake:

% radioiodine uptake was measured for all foci of uptake. % uptake was measured by a thyroid probe or a computerized region-of-interest analysis with a digital gamma camera, or both.

Note: any residual radioiodine uptake from the Thyrogen scan measured prior to the WD scan was subtracted from the uptake measured for the WD scan.

RESULTS:

A total of 152 patients were enrolled from 11 investigational sites. Demographics was as follows:

Gender:	106 (70%) female
	46 (30%) male
Age:	mean- 44 yrs. (range 20-84 yrs.)
Histology:	papillary- 110 patients (72%)
	pap/foll variant- 23 (15%)
	follicular- 16 (11%)
	Hurthle cell- 3 (2%)
Status @ enrollment:	post thyroidectomy/pre-ablation 29(19%)
	post thyroidectomy & ablation 122(80%)
	post thyroidectomy w/o ablation 1 (1%)
	(note: this was a patient who had been ablated for Graves Disease and subsequently was diagnosed with papillary cancer);
thyroidectomy status:	near total 144 (95%)
	subtotal 4 (3%)
	hemi 3 (2%)

previous radioiodine therapy: 101 (66%)

A total of 130 patients completed the study. Of those who did not complete the study, there were 14 patients excluded for protocol violations (7 for insufficiently suppressed TSH levels at enrollment, 6 whose TSH levels did not reach 25 mU/L during WD but were scanned, and 1 patient who was enrolled while participating in another investigational study). Of the remaining 8 who did not complete the study, 4 withdrew due to adverse events and 4 withdrew for personal reasons.

Efficacy:

ITT (Intent-to-Treat Population):

There were 138 scan pairs available for evaluation in the ITT population.

Equivalence of Cancer Classification: Consensus of 3 IRS:

ITT: Side-by-Side Comparison:

# Patients in ITT Population with Eligible Scans:	n= 138
Concordance:	n= 116[A] (84%)
Discordance:	n= 22 (16%)
Thyr> WD[B]:	n= 3 (2%)
WD > Thyr[C]:	n= 19 (14%)
p value (2-tailed sign test)	**p= < 0.001**

A= **of these 116 scan pairs which were read as "concordant" based on a side-by-side comparison of the scans, 11 pairs were actually discordant when read individually by the IRS.**

B= Thyr > WD means the Thyrogen scan showed a greater # of lesions or extent of disease

C= WD > Thy means the WD scan showed a greater # of lesions or extent of disease

These 11 scan pair readings which were discordant when read individually but not when read side-by-side were as follows:

	Thyrogen Scan Stage	WD Scan Stage
Patient 206	Stage 4[A]	Stage 1[A]
Patient 303	0	1
Patient 309	1	2
Patient 325	0	1
Patient 711	3[B]	0
Patient 716	4	3
Patient 1004	0	1
Patient 1103	0	2
Patient 1104	3	1
Patient 1105	0	3
Patient 1106	1[C]	2[C]

A= scan pair for patient 206 rated as "concordant" in the side-by-side comparison based on thyroid bed uptake only. Right shoulder images which had shown a focus of uptake on the Thyrogen scan were not included in the WD scan series. A subsequent CT

scan was negative for metastases.
B= The Thyrogen scan went to panel review and the consensus was that they could not distinguish between saliva in the esophagus and mediastinal metastases. The decision was to rate the scan pair as "concordant".
C= The panel's decision was to rate this scan pair as "concordant" but they could not tell if the scans were positive for stage 1 or stage 2 disease.

Note: the nature of the discordant scan pairs will be addressed in the efficacy evaluable analysis.

Efficacy Evaluable:

Using the efficacy evaluable population, there were 127 scan pairs available for analysis.

Equivalence of Cancer Classification: Consensus of 3 IRS:
Efficacy Evaluable: Side-by-Side Comparison:

patients with eligible scans n= 127

Concordant:n= 106 (83%) (stage 0: 65/66, stage 1: 30/46, stage 2: 6/9, stage 3: 3/4, stage 4: 2/2)

Discordant:n= 21 (17%)
Thy > WD: n= 3
WD > Thy n= 18
p value = < 0.05

The 21 discordant scan pairs in the side-by-side comparison were as follows:

	Thyrogen Scan Stage	WD Scan Stage
Thyr stage>WD stage (n=2)	2 stage 1[A]	2 stage 0
1 more lesion on Thyrogen scan(n=1)	1 stage 1	1 stage 1
WD stage> Thy stage (n= 13)	9 stage 0	9 stage 1[B]
	2 stage 0	2 stage 2[C]
	1 stage 0	1 stage 3
	1 stage 1	1 stage 2
# lesions greater or uptake seen more clearly defined on WD scan (n= 5)	1 stage 0	1 stage 0[D]
	4 stage 1	4 stage 1[E]

Note: the 1 additional scan pair in the ITT analysis where the WD scan was > Thyrogen scan, showed an additional focus of uptake in the thyroid bed.

Note: there were only 15/127 (12%) patients who had scans that

were positive for metastatic disease (class ≥2).
A= ½ patients was rx'd with ^{131}I and post-rx. scan was negative.
B= 5/9 patients were rx'd and the post-therapy scan was positive.
C= Both patients were rx'd and the post-rx. scan was positive.
D= 2/3 IRS commented that the Thyrogen and WD scans were discordant although the consensus was that they were both stage 0. One IR stated that the WD scan was "a much better study". The other IR stated that there might be an abnormal focus of uptake in the chest on the WD scan but it was poorly defined.
E= 2/4 patients were rx'd and post-rx. scans were negative.

Equivalence of Cancer Classification in Patients with Positive Scans: Consensus of 3 IRS: Side-by-Side Comparison:

	ITT n= 65	Efficacy Evaluable n= 61
Concordance	44 (68%)	41 (67%)
Discordance Thy > WD WD > Thy p value	21 (32%) 3 18 0.001	20 (33%) 3 17 <0.05

Equivalence of Cancer Classification in Recent Thyroidectomy Patients vs. Follow-up Patients: IRS: Side-by-Side Comparison:

	ITT n= 137		Efficacy Evaluable n=126	
	Recent n=25	F/U n= 112	Recent n=22	F/U n= 104
Concordant	20 (80%)	95 (85%)	18 (82%	87 (84%)
Discordant Thy > WD WD > Thy p value	5 (20%) 2 3 1.000	17 (15%) 1 16 <0.001	4 (18%) 2 2 1.000	17 (16%) 1 16 <0.001

A comparison of the scan readings among the 3 IRS revealed that individually, the IRS rated the scans as discordant in 24 (19%), 41 (32%) and 32 (25%) cases, respectively. This difference in individual reviewer rating of the scans illustrates the subjective nature of interpreting the scan results.

Study scan efficacy results were also examined for any site to site variability which may have confounded the study results. There were no significant site to site differences ($p > 0.05$, Fisher's Exact Test (2 tailed).

Radioiodine Uptake, Retention and Half-Life- Hypothyroid vs. Euthyroid State:

In a subset of patients who had undergone a total thyroidectomy, with paired quantitative uptake measurements, the mean thyroid bed uptake of ^{131}I was significantly higher after WD than after Thyrogen:

thyroid probe analysis- for WD: 0.4±0.7% vs. for Thyrogen: 0.3±0.7%, $p < 0.002$ in 48 patients and

region-of-interest analysis- for WD: 0.5±0.9% vs. for Thyrogen: 0.3±0.6%, $p<0.01$ in 32 patients.

In 33 patients, serum ^{131}I levels and whole body retention were measured 48 hrs. after the administration of the tracer dose for both the Thyrogen and WD scans. The mean thyroidal uptake, whole body ^{131}I retention and serum ^{131}I levels were significantly greater ($p < 0.0001$) during WD than after Thyrogen by factors of 2.40, 2.58 and 3.00, respectively. However, when the mean thyroidal uptake was corrected for the difference in whole body ^{131}I retention, this difference disappeared.

In a subset of these 7 patients, serial whole body ^{131}I retention was measured prior to the administration of the tracer dose and at 2, 24 and 48 hrs. The whole body ^{131}I retention half-life and area under the curve (AUC) increased 1.72 and 1.42 x, respectively, during WD compared to Thyrogen.

In a subset of 5 of these patients, serum ^{131}I was measured prior to the administration of the tracer dose and at 2, 24 and 48 hrs. The serum ^{131}I half life and AUC increased 1.50 and 1.51x, respectively, during WD compared to Thyrogen.

Thus, the clearance of ^{131}I in euthyroid patients treated with Thyrogen is ~twice that observed during the hypothyroid state during WD. This increase in ^{131}I bioavailability in hypothyroid patients explains the significantly greater quantitative thyroidal uptake during WD and, hence, the greater sensitivity of the WD scan compared to the Thyrogen scan.

Quality of Life:

As expected, patients experienced significantly more hypothyroid symptoms after WD compared to the euthyroid Thyrogen phase as assessed by both the POMS and Billewicz scale.

Thyroglobulin (Tg) Response:

Tg was not prospectively identified as a study variable in protocol TSH92-0601. Although Tg was measured in all study patients 24 hrs. after the second dose of Thyrogen, the value of the data is limited because the levels reported were not measured in a central laboratory, and, therefore, the data are not controlled for assay variability between institutions due to differences in assay sensitivity. Furthermore, the results of a subsequent Tg kinetic study revealed that 24h is a suboptimal

time to measure Thyrogen Tg.

In a subset of 35 patients, serial Thyrogen Tg levels were measured at 24, 48, 72 and 96 hrs. after Thyrogen administration. No formal analysis was done on this data and one must be cautious not to draw definitive conclusions due to the limitations discussed above. However, 2 comments can be made:

1. In some patients, the Thyrogen Tg levels were higher at 48-96 hrs. than at 24 hrs. and

2. There appears to be no correlation between Thyrogen Tg and WD Tg. At any of these given time points for any given patient, the Thyrogen Tg may be similar to, less than or greater than the corresponding WD Tg.

24h post Thyrogen Tg levels were available in a subset of 13 patients who had undergone a total thyroidectomy and been ablated, and were Tg antibody negative, and had a positive post-therapy scan. In 7/13 patients, Tg levels on THST, Thyrogen and WD were all > 10 ng/ml. Of the remaining 6 patients, Tg on THST, Thyrogen and WD, was undetectable (< 1 ng/ml) in 1 patient. Of the remaining 5 patients, WD Tg was > 10 ng/ml in 4 patients, but the corresponding Thyrogen Tg was > 10 ng/ml in only 1 of these 4 patients. Again, as noted above, there was no correlation between Thyrogen Tg and WD Tg.

SAFETY:

Deaths:

There was 1 death in this study. A 69 yr. old F expired from pulmonary embolism and recurrent thyroid cancer which had infiltrated the trachea and surrounded a carotid artery. She also had a history of asthma. Death occurred 6 days after receiving her second Thyrogen injection. The death was determined not to be related to Thyrogen.

Drop-outs Due to AES:

There were 4 patients who did not complete the study due to AES:

1. A 42 yr. old F c/o **nausea and dizziness** after receiving her first dose of Thyrogen. These events were deemed by the investigator to be definitely related to Thyrogen. She discontinued the study prior to receiving her second dose.

2. A 56 yr. old M c/o **nausea and vomiting** after receiving 2 doses of Thyrogen. The patient had been experiencing these symptoms prior to study participation. The investigator deemed these symptoms to be possibly related to Thyrogen and discontinued the patient from the study.

3. A 38 yr. old F discontinued the study after experiencing **flu-like symptoms** of headache, diarrhea, nausea and vomiting. The investigator attributed these symptoms to a viral GE rather than to Thyrogen.