Specific FN 72h Thyrogen Tg levels compared to WD Tg level (Thyrogen Tg/WD Tg) Grouped by Cut-off and Reference Scan Class:

@ 1 ng/ml cut-off
72h Thyrogen Tg/WD Tg gp. by ref. scan class

class 0:
none

class 1:
5 pts. both Thyrogen Tg and WD Tg <1 ng/ml^A

@ 2 ng/ml cut-off
72h Thyrogen Tg/WD Tg gp. by ref. scan class

class 0:
1.0/6.3 ng/ml

class 1:
1.8/6.1 ng/ml
1.3/7.0 "
1.3/4.0 "
1.8/8.5 "
1.2/0.5 "
1.0/0.9 "
5 pts. both Thyrogen Tg and WD Tg <1 ng/ml^A
2 pts. Thy Tg & WD Tg >1-<2 ng/ml^A

@ 3 ng/ml cut-off
72h Thyrogen Tg/WD Tg gp. by ref. scan class

class 0:
none

class 1:
1.8/ 6.1 ng/ml
1.3/ 7.0 "
1.3/ 4.0 "
1.8/ 8.5 "
1.2/ 0.5 "
1.0/ 0.9 "
2.9/19.4 "
2.8/ 7.6 "
2.1/ 1.8 "
5 pts. both Thyrogen Tg & WD Tg <1 ng/ml^A
2 pts. Thy Tg & WD Tg >1-<2 ng/ml^A

class 2:
2.0/16.5 ng/ml

A= These Thyrogen Tg levels were FNS because by the ref. scan std., disease was present (ref. scans were class 1), but these Thyrogen Tgs were < cut-off.

The above tabulation of FN Thyrogen Tg/WD Tg levels demonstrates that there is no correlation between Thyrogen Tg and WD Tg. For any given cut-off, Thyrogen Tg could be equivalent to, less than or greater than the corresponding WD Tg; and if greater than or less than, to highly variable degrees. Therefore, for a given Thyrogen Tg, we cannot predict what the corresponding WD Tg would have been, had the patient been withdrawn.

Arm II: FN 72h Thyrogen Tg-/+ scan patients using the **same Tg cut-off** to compare to WD, grouped by Tg cut-off and the reference std. scan class:

[Note: the Ref. Std. is a WD Tg ≥ the given cut-off- 1, 2, 3, 5, or 10 ng/ml- or a class ≥ 1 WD or post-rx. scan] [note: R= recently thyroidectomized but pre- ^{131}I ablation, f/u= follow-up patient: s/p surgical and ^{131}I ablation]:

Tg cut-off (ng/ml)	# (%)*FN Thyrogen Tg patients by reference scan class (Note: the denominator for # FN at each ref. scan class is # TP by ref. std.)	# (%)**FN Thyrogen Tg + scan patients by reference scan class (Note: the denominator for # FN at each ref. scan class is # TP by ref. std.)
1 ng/ml	7/71* (10%) class 0 n= 2/18 f/u class 1 n= 5/29 (1R, 4 f/u) class 2 n= 0/5 class ≥ 3 n= 0/18 inadequate scans n= 0/1	3/70** (4%) class 0 n= 2/18 f/u class 1 n= 1[A]/29 f/u class 2 n= 0/5 class ≥3 n= 0/18
2 ng/ml	16/68* (24%) class 0 n= 3/15 f/u class 1 n=13/29 (3R, 10 f/u) class 2 n= 0/5 class ≥3 n= 0/18 inadequate scans n= 0/1	5/67** (7%) class 0 n= 3/15 f/u class 1 n= 2[A]/29 f/u class 2 n= 0/5 class ≥3 n= 0/18
3 ng/ml	20/65* (31%) class 0 n= 3/12 f/u class 1 n=16/29 (5R, 11 f/u) class 2 n= 1[C]/5 f/u class ≥3 n= 0/18 inadequate scans n= 0/1	5/64** (8%) class 0 n= 3/12 f/u class 1 n= 2[A]/29 f/u class 2 n= 0/5 class ≥3 n= 0/18
5 ng/ml	24/64* (38%) class 0 n= 4/11 f/u class 1 n=19/29 (8R, 11 f/u) class 2 n= 1[C]/5 f/u class ≥ 3 n= 0/18 inadequate scans n= 0/1	6/63** (10%) class 0 n= 4[B]/11 f/u class 1 n= 2[A]/29 f/u class 2 n= 0/5 class ≥3 n= 0/18
10 ng/ml	27/59* (46%) class 0 n= 2/6 f/u class 1 n=22/29 (9R, 13 f/u) class 2 n= 1[C]/5 f/u class ≥ 3 n= 2[C]/18 f/u inadequate scans n= 0/1	6/58** (10%) class 0 n= 2[B]/6 f/u class 1 n= 2[A]/29 f/u class 2 n= 0/5 class ≥ 3 n= 2[C]/18 f/u

* = % patients in whom Thyrogen Tg -/+ scan failed to detect remnants/cancer identified by the reference standard= FN rate.

	+= TP by ref. std. were distributed by reference scan class as follows:					++= TP by ref. std. were distributed by reference scan class as follows:				
	@1	@2	@3	@5	@10	@1	@2	@3	@5	@10
class 0	34	27	24	21	19	34	27	24	21	19
class 1	20	20	20	20	20	20	20	20	20	20
class 2	4	4	4	4	4	4	4	4	4	4
class ≥3	5	5	5	5	5	5	5	5	5	5
inadequate	1	1	1	1	1	1	1	1	1	1

Note: there were 23 patients total in arm II who had metastatic disease confirmed by scan.

A= In these patients, the Thyrogen scan was negative for cancer localized to the thyroid bed, detected by the WD scan.

B= Although the post-rx. scan was negative in 1 of these patients, the **lymph node biopsy** done post-study was positive for **metastatic cancer**. The **Thyrogen Tg/WD Tg** in this patient was **3.9/37.8** ng/ml.

C= Combining all cut-offs, **Thyrogen Tg was a FN in 3 patients** in whom **metastatic disease** was detected by the post-rx. scan. Metastatic disease was missed by the Thyrogen scan in these 3 patients and was detected by the WD scan in 1. The Thyrogen Tg levels in these patients were **2.0, 7.0 and 8.7 ng/ml.** The corresponding **WD Tg levels** in these patients were **16.5, 108 and 45 ng/ml**, respectively. Only 2 of these patients were classified as FNS when the Thyrogen Tg and scan were combined. This was because, in the other patient, the Thyrogen scan was class 1 and the ref. scan std. was class ≥ 1; had the ref. scan std. been class ≥ 2, this patient would have been a FN.

Additional comments:

Thyrogen Tg missed remnants/cancer identified by the reference standard in 10-46% patients between the 1-10 ng/ml cut-offs, respectively.

In patients with class 1 disease detected by the reference scan, the Thyrogen Tg was a FN in 5-22 patients (7-38%) between the cut-offs of 1-10 ng/ml, respectively.

Thyrogen Tg missed metastatic disease confirmed by the reference scan in 3 patients, one of whom had a Thyrogen Tg level of only 2.0 ng/ml (corresponding WD Tg level was 16.5 ng/ml). (See footnote C for further details).

The combination of the Thyrogen Tg and scan missed cancer identified by the reference standard in 4-10% patients between the cut-offs of 1-10 ng/ml.

The combination of the Thyrogen Tg and scan missed cancer identified by the reference scan as localized to the thyroid bed, in 1-2 patients between the cut-offs of 1-10 ng/ml, respectively.

The combination of the Thyrogen Tg and scan missed metastatic disease identified by the reference scan in 2 patients

at the 10 ng/ml cut-off.

Specific FN 72h Thyrogen Tg levels Compared to WD Tg (Thy Tg/WD Tg) Grouped by Cut-off and the Reference Scan Class:

n= 7 FN @ 1 ng/ml Thy Tg/WD Tg	n= 16 FN @ 2 ng/ml Thy Tg/WD Tg	n= 20 FN @ 3 ng/ml Thy Tg/WD Tg	n= 24 FN @ 5 ng/ml Thy TG/WD Tg	n= 27 FN @ 10 ng/ml Thy Tg/WD Tg
class 0:	**class 0:**	**class 0:**	**class 0:**	**class 0:**
0.8/1.2ng/ml	1.0/ 6.3ng/ml	1.0/ 6.3ng/ml	1.0/ 6.3ng/ml	9.6/17.2ng/ml
0.8/1.3 :	1.1/ 2.7 "	2.1/ 9.6 "	2.1/ 9.6 "	3.9/37.8 "
	1.0/ 2.0 "	2.3/ 4.4 "	3.9/37.8 "	
			3.3/ 9.4 "	
class 1:	**class 1:**	**class 1:**	**class 1:**	**class 1:**
5 pts. both Thy Tg & WD Tg <1[A]	1.8/ 6.1ng/ml	1.8/ 6.1ng/ml	1.8/ 6.1ng/ml	1.8/ 6.1ng/ml
	1.3/ 7.0 "	1.3/ 7.0 "	1.3/ 7.0 "	1.3/ 7.0 "
	1.3/ 4.0 "	1.3/ 4.0 "	1.3/ 4.0 "	1.3/ 4.0 "
	1.8/ 8.5 "	1.8/ 8.5 "	1.8/ 8.5 "	1.8/ 8.5 "
	1.2/ 0.5 "	1.2/ 0.5 "	1.2/ 0.5 "	1.2/ 0.5 "
	1.0/ 0.9 "	1.0/ 0.9 "	1.0/ 0.9 "	1.0/ 0.9 "
	5 pts. both Thy Tg & WD Tg <1[A]	2.8/ 7.6 "	2.8/ 7.6 "	2.8/ 7.6 "
		2.9/19.4 "	2.9/19.4 "	2.9/19.4 "
	2 pts. with similar Thy & WD Tgs[A]	2.1/ 1.8 "	2.1/ 1.8 "	2.1/ 1.8 "
		5 pts. both Thy Tg & WD Tg <1[A]	3.7/ 4.7 "	3.7/ 4.7 "
			4.0/11.2 "	4.0/11.2 "
		2 pts. with similar Thy & WD Tgs[A]	5 pts. both Thy Tg & WD Tg <1[A]	7.7/30.6 "
				5.1/11.4 "
			3 pts. with similar Thy & WD Tgs[A]	5 pts. both Thy Tg & Wd Tg <1[A]
				4 pts. with similar Thy & WD Tgs[A]
	class 2:	**class 2:**		**class 2:**
	2.0/16.5ng/ml	2.0/16.5ng/ml		2.0/16.5ng/ml
				class ≥ 3:
				8.7/ 45.4ng/ml
				7.0/108.4 "

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A= These Thyrogen Tg levels were FNS because by the ref. scan std., disease was present and these Thyrogen Tg levels were < the given cut-off.

The above tabulation of FN Thyrogen Tg/WD Tg levels demonstrates that there is no correlation between Thyrogen Tg and WD Tg. For any given cut-off, Thyrogen Tg could be equivalent to, less than or greater than the corresponding WD Tg; and if greater than or less than, to highly variable degrees. Therefore, for a given Thyrogen Tg, we cannot predict what the corresponding WD Tg would have been, had the patient been withdrawn.

At the end of this review is enclosed a scatter plot of WD Tg vs. Thyrogen Tg in patients with class 0 and class 1 WD scans. They demonstrate that there is no correlation between Thyrogen Tg and WD Tg.

A Comparison of FNS Between Tg on THST and the 72h Thyrogen Tg by cut-off and Reference scan class:

The following points made by **Schlumberger** in his recent review article: "Papillary and Follicular Thyroid Carcinoma" **[NEJM 338(5):297-306, 1998**) will be applied to my discussion of the following table which compares the FNS on Tg on THST to Thyrogen Tg:

1. A sensitive Tg assay should be used- i.e. one with lower limits of detectability of ≤ 1 ng/ml
2. A **detectable Tg on THST** is defined as a **level at or above the lower limits of detectability of the assay**
3. **A detectable serum Tg on THST warrants withdrawal** to measure Tg. Whether or not a scan is also performed depends on the tumor stage and the clinical likelihood of recurrent or persistent disease.

Since in the TSH95-0101 Thyrogen study, a very sensitive Tg assay was used, the # of FN Tg levels on THST should be evaluated based on the lower limit of detection of the assay- in this case, 0.5 ng/ml. However, since the **sponsor** did not distinguish between Tg levels reported by the central lab as <0.5 ng/ml (i.e. undetectable) vs. those reported as 0.5 ng/ml, but **recorded all <0.5 or 0.5 ng/ml values as <0.5 ng/ml in their data listings**, we will define a Tg level on THST as "detectable" when it is >0.5 ng/ml. **Therefore, the # of Tg levels being reported here as FNS, is somewhat of an overestimate.**

Comparison of FNS Between Tg on THST and the 72h Thyrogen Tg by cut-off and Reference scan class:

Using the **same Tg cut-off** to compare Tg on THST and Thyrogen Tg to WD Tg: (Reference std: WD Tg ≥ the given cut-off or a class 1 WD or post-rx. scan):

Arm I:

Tg cut-off (ng/ml)	# (%) FN Tg on THST grouped by reference scan class	# (%) FN 72h Thyrogen Tg grouped by reference scan class
0.6 ng/ml	20/69 (29%) class 0 n= 9 class 1 n= 8 (3R, 5 f/u) class 2 n= 1 f/u[A] class 3 n= 1 f/u[B] inadequate scan n= 1[C]	8/69 (12%) class 0 n= 3[E] class 1 n= 5 (1R, 4 f/u)

1 ng/ml	29/64 (45%) class 0 n= 15 class 1 n= 10(5R, 5 f/u) class 2 n= 2 f/u[D] class ≥ 3 n= 1 f/u[B] inadequate scan n= 1[C]	17/64 (27%) class 0 n= 9[F] class 1 n= 8 (3R, 5 f/u)

A and B= In these **2 patients** with documented **metastases** on the post-rx. scan, the **Tg on THST was ≤ 0.5 ng/ml.** The **corresponding Thyrogen Tg levels were 5.4 ng/ml,** in the patient with localized metastases to the neck, **and 6.9 ng/ml** in the patient with distant metastases. **The WD Tgs were 25.3 and 11.8 ng/ml, respectively.**
C= Although the **WD Tg was 54 ng/ml** in this patient, the **Tg on THST was ≤ 0.5 ng/ml and the Thyrogen Tg was only 2.5 ng/ml.**
D= The Tg levels in the **additional patient** with documented **neck metastases** by post-rx. scan at the 1 ng/ml cut-off were: **Tg on THST 0.9 ng/ml** (i.e. detectable Tg by this sensitive assay), **Thyrogen Tg 5.2 ng/ml and WD Tg was 22 ng/ml.**
E= 1 of these 3 patients with an undetectable Thyrogen Tg (≤ 0.5 ng/ml), 1 had a detectable Tg on THST (0.7 ng/ml).
F= 1 of these 9 patients in whom Thyrogen Tg was < 1 ng/ml, had a Tg on THST > 1 ng/ml (1.2 ng/ml).
Comments on the above table:

a. There are less FNS on Thyrogen than on Tg on THST. However, since we do not know in how many patients the Tg on THST was at the lower limits of detection (i.e. 0.5 ng/ml), it is not possible to state the true # of patients in whom Tg on THST was undetectable.

b. <u>Classifying the 20 FN Tg levels on THST (i.e. levels ≤ 0.5 ng/ml) and the 7 FN Thyrogen Tg levels (≤ 0.5 ng/ml) by WD Tg level and reference scan class:</u>

Arm I:	Tg on THST ≤ 0.5 ng/ml N= 20 FN	Thyrogen Tg ≤ 0.5 ng/ml N= 8 FN
WD Tg <2 ng/ml & ref. scan class ≤ 1 (n=22)	10	5
WD Tg ≥ 2-<10 ng/ml & ref. scan class ≤ 1(n=11)	5	2
WD Tg ≥ 10 but ref. scan was negative (n=18)	2	1
WD Tg ≥ 10 ng/ml & ref. scan class 1 (n=6)	0	0
Metastatic disease by ref. scan (n= 9)	2	0
Metastatic disease by + lymph node biopsy (n=2)	0	0
WD Tg ≥ 10 but ref.		

scans were inadequate(n= 1) 1 0

Arm II:

Tg cut-off (ng/ml)	# (%) FN Tg on THST grouped by reference scan class	# (%) FN 72h Thyrogen Tg grouped by reference scan class
0.6 ng/ml	17/68 (25%) class 0 n= 4[A] class 1 n= 12(4R, 8 f/u) class 2 n= 1 f/u[B]	4/68 (6%) class 1= 4[C] (1R, 3 f/u)
1 ng/ml	25/66 (35%) class 0 n= 8 f/u[A] class 1 n=16(6R, 10 f/u class 2 n= 1 f/u[B]	7/66 (11%) class 0 n= 2[D] class 1 n= 5[C, E](1R, 4f/u

A= Cervical lymph node biopsy post-study was **+ for cancer. Tg on THST/Thyrogen Tg/WD Tg were ≤ 0.5/3.9/37.8 ng/ml,** respectively.
B= Tg levels in patient with neck metastases on post-rx scan were Tg on THST/Thyrogen Tg/WD Tg: ≤ 0.5/2.0/16.5 ng/ml, respectively.
C= Tg on THST: 1.1 ng/ml in one pt. with Thyrogen Tg ≤ 0.5 ng/ml.
D= In 1 of these patients with a negative WD scan, the **WD Tg was 9.0 ng/ml,** but the corresponding **Thyrogen Tg was 21.9 ng/ml.**
E= In 1 of these patients with a class 1 WD scan, the **WD Tg was 2.3 ng/ml,** but the corresponding **Thyrogen Tg was 16.5 ng/ml.**

Note: There are less FNS on Thyrogen than on Tg on THST. However, since we do not know # of patients in whom Tg on THST was detectable at 0.5 ng/ml, it is not possible to state the true # of patients in whom Tg on THST was undetectable (i.e. <0.5).

Classifying the 17 FN Tg levels on THST (i.e. levels ≤ 0.5 ng/ml) and the 4 FN Thyrogen Tg levels (≤ 0.5 ng/ml) by WD Tg level and reference scan class:

Arm II:	Tg on THST ≤ 0.5 ng/ml N= 17 FN	Thyrogen Tg ≤ 0.5 ng/ml N= 4
WD Tg <2 ng/ml & ref. scan class ≤ 1 (n=15)	9	4
WD Tg ≥ 2-<10 ng/ml & ref. scan class ≤ 1(n=16)	4	0
WD Tg ≥ 10 but ref. scan was negative (n=3)	0	0
WD Tg ≥ 10 ng/ml & ref. scan class 1 (n=9)	2	0
Metastatic disease by ref. scan (n=21)	1	0

Metastatic disease by + lymph node bx. or + CT scan (n= 3)	1	0
WD Tg ≥ 10 but ref. scans were inadequate (n= 1)	0	0

False Positive Thyrogen Tg -/+ scan values by the Diagnostic Utility Analyses:

FP Thyrogen Tg levels:

There were 2 patients in arm II, in whom the **Thyrogen Tg was > 10 ng/ml** and the **corresponding WD Tg was < 10 ng/ml:**

Patient #708 f/u patient:

48h Thyrogen Tg/72h Thyrogen Tg/Wd Tg= 20.8/21.9/9.0 ng/ml;

Thyrogen and WD scans were negative and patient was not rx'd

Patient #1311: recently thyroidectomized patient:

48h Thyrogen Tg/72h Thyrogen Tg/WD Tg= 17.1/16.5/2.3 ng/ml;

Thyrogen and WD scans were both class 1; patient was not treated because the WD Tg indicated that only a small amount of thyroid tissue was present.

Note: the Tg on THST was undetectable (<0.5 ng/ml) in both patients.

FP Thyrogen Tg + scan patients:

Arm I:

Of the 5 patients in whom the Thyrogen Tg + scan was FP, 2 are most notable: f/u patients- #702 and 1227, both in whom the Thyrogen scans were positive for cancer localized to the thyroid bed but the WD scans were negative and neither patient was treated. The Thyrogen Tg/WD Tg levels in these patients were: 0.5/0.8 ng/ml and 2.7/2.8 ng/ml, respectively.

Arm II:

Of the 8 patients in whom the Thyrogen Tg + scan was FP, 2 are particularly noteworthy:

In patient #1612, the Thyrogen scan was positive for cancer localized to the thyroid bed but the WD scan was negative. The Thyrogen and WD Tg levels were both undetectable (< 0.5 ng/ml) and the patient was not treated.

In patient #1711, the Thyrogen scan was positive for metastatic disease (class 2A) but the WD scan was negative; both Thyrogen and WD Tg levels were < 1 ng/ml and the patient was not treated.

On February 24, 1998, Dr. Sobel, Dr. Orloff, Dr. Castillo (statistician), Mr. McCort and myself had a lengthy t-con (~1.5 hrs.) with Genzyme to discuss the problems with Thyrogen (refer to minutes of this t-con for details). In summary, the firm was informed that:

1. Their statements both in the NDA and the draft label that

a given Thyrogen Tg level (of 1, 2 or 3 ng/ml) "corresponds" to a given WD Tg level (i.e. 2, 5, or 10 ng/ml, respectively) is not correct because there is no correlation between Thyrogen Tg and WD Tg. The sponsor admitted that this is true.

2. Because no correlation exists, we cannot interpret a given Thyrogen Tg level in relation to WD Tg.

3. Dr. Sobel inquired if the firm had any plans to study a more prolonged period of Thyrogen administration. They responded in the negative.

4. The firm stated they would consult with their experts regarding how this product can be used and rewrite the draft label to make it less statistical and more clinically relevant.

On March 16, 1998, Genzyme sent in a "Position Paper" which included algorithms for the proposed uses of Thyrogen and also, revised draft labeling. These algorithms pertained to the use of Thyrogen as an alternative diagnostic to withdrawal to detect remnants and/or cancer. They also included proposed uses for Thyrogen as a screening test alternative or, in addition, to Tg on THST for the follow-up of patients with thyroid cancer. These algorithms will be critiqued in the Evaluation section of this review (see page 67). In the revised draft labeling, the sponsor deleted statements that a given Thyrogen Tg level (of 1, 2 or 3 ng/ml) "corresponds" to a given WD Tg level (i.e. 2, 5, or 10 ng/ml, respectively). They also revised the Indications and Usage section from recommending a Thyrogen scan and/or serum Thyrogen Tg to detect remnants and/or cancer to performance of both the Thyrogen scan and Tg for diagnostic purposes. There were several incorrect statements made by the sponsor in this position paper which I will point out here:

1. The sponsor stated a Tg level $\geq$2 ng/ml defined the presence of remnants/cancer in study TSH95-0101. They stated that although the assay had a lower limit of detectability of 0.5 ng/ml, the "interassay precision of this assay across a two month period was 18.8% using a 1.5 ng/ml standard." However, in study TSH95-0101, all the Tg samples were assayed in a single run. Furthermore, several successfully ablated, Tg Ab negative patients had scan detectable remnants/cancer but their WD Tg levels were <2 ng/ml.

2. Diagnostic utility analyses were performed by the sponsor using the same reference standard as in the NDA but using a Tg cut-off of 2 ng/ml only to compare Thyrogen to WD and Thyrogen to Tg on THST. The problems with these analyses are two-fold:

a. Selecting only a low Tg cut-off to directly compare the performance of Thyrogen to WD, using the reference standard chosen post-hoc, masks the true difference in performance between Thyrogen and WD. It is at the higher cut-offs where it is most evident that with Thyrogen we are not achieving the high Tg levels we are getting on WD (see my diagnostic utility analyses,

tables 3A-B and 4A-B, pages 40-41 of this review).

b. It is inappropriate to disregard Tgs level <2 ng/ml when comparing Thyrogen to Tg on THST when a Tg assay is used which has a lower limit of detection below 2 ng/ml. In study TSH95-0101, the Tg assay used had a lower limit of detection of 0.5 ng/ml. Per Schlumberger (NEJM 338(5): 297-306, 1998), a Tg level on THST which is at or above the lower limits of detection of the assay is significant.

Additional Comments:

a. When rating a scan pair as concordant, the IRS were asked if there was a difference in the number and distribution of the lesions that could potentially alter the clinical management of the patient. In no patient, in either treatment arm, was such a consensus reached by the 3 IRS that this was the case.

b. There were only 3 patients in this study who did not achieve the minimal TSH level after WD (defined here as a TSH level of 25 mU/L) required as sufficient for scanning. Because this number was so small, an additional scan equivalence analysis excluding these patients was not performed.

c. Patients with both 48h and 72h scans:

There were 2 patients in arm I and 15 patients in arm II with both 48h and 72h scans and a consensus IR rating.

The 72h scan was done after the 48h Thyrogen scan only in 1 patient, and after the WD scan only in 4 patients. This additional scan was concordant with the 48h classification in all 5 patients.

In 12 patients, 48h and 72h scans were available for both the Thyrogen and WD scan series. The 72h scan was concordant with the 48h scan in 9/12 patients. In the remaining 3 patients, the 72h scan revealed metastatic disease or a higher class of metastatic disease than that seen on the 48h scan, confirmed in all 3 cases, by a post-rx. scan. The scan classes for these 3 patients were:

	Thyrogen scan Class 48h/72h	WD scan Class 48h/72h	Post-rx. scan Class
Patient #1504	0 /3B	1/3B	3B
Patient #1513	3D /4A	3D/4A	4A
Patient #1525	0/4A	0/4A	4A

d. Distinction Between Thyroid Remnant and Localized Cancer Recurrence:

The IRS were asked if, in patients with class 1 scans, they were able to distinguish between thyroid remnant and cancer by comparing the study diagnostic scan to the most recent scan conducted prior to study enrollment. This comparison was difficult because many of the most recent scans were of poor technical quality. In only 6 patients, were the IRS able to make this distinction. In 5, they rated the class 1 uptake as remnant and, in 1, as local disease recurrence.

SAFETY:

The lack of a placebo control group and the fundamental medical difference between the Thyrogen and WD phases precludes

making a definitive assessment of Thyrogen relatedness to the adverse events reported in this study.

Deaths:

None

Drop-outs due to Adverse Events:

None

Overall Adverse Events:

In arm I, 46/117 patients (39%) reported a total of 73 events; in study arm II, 33/112 patients (30%) reported a total of 69 events. The difference between the two treatment arms in the % of patients who experienced adverse events was not statistically significantly different.

Adverse Events (AES) Occurring in >5% of patients During the Thyrogen Phase:

Headache, nausea and asthenia were the most commonly reported AES. The frequency was as follows:

Adverse Event	Arm I (n= 117)	Arm II (n= 112)	Total (n= 229)
Headache	13 (11%)	8 (7%)	21 (9%)
Nausea	9 (8%)	5 (5%)	14 (6%)
Asthenia	6 (5%)	2 (2%)	8 (4%)

Adverse Events (AES) Occurring in ≥1% but <5% of patients during the Thyrogen phase:

2-6/229 patients (1-3%), combining both treatment arms, experienced the following AES:
vomiting and paresthesias (3% each),
nausea and vomiting, pain, fever, flu syndrome (each 2%),
dyspepsia, dizziness, abdominal pain and palpitations (1% each)

Serious AES:

Serious adverse events were reported in 4 patients. None were attributed to Thyrogen by the investigators.

Arm I:

1. Heart palpitations and chest pressure were reported in a 54 yr. old F with prior episodes of chest pressure. These AES were reported 30 days after Thyrogen administration and 15 days into the WD phase.

2. Palpitations, chest pain, light-headedness and left hand numbness were reported in a 36 yr. old F during the WD phase and 26 days after Thyrogen administration. The sponsor stated the patient had a negative cardiac work-up.

3. Syncope was reported in a 51 yr. old F during the eighth day of the WD phase and 52 days after Thyrogen administration. Syncope was attributed to toxicity from her Paxil, secondary to a hypothyroid associated decrease in drug clearance.

Arm II:

A 62 yr. old F with a hx. of metastatic papillary thyroid cancer, hypertension and diabetes mellitus, was hospitalized with fever, uncontrolled diabetes mellitus, uncontrolled hypertension, nausea and vomiting, which occurred

during the WD phase and 26 days after initial Thyrogen administration. An UGI evaluation revealed Candida esophagitis, gastritis and a bulbar ulcer.

Other Adverse Events Listed by the Sponsor as Significant:

Paresthesias were reported in 6/229 patients (3%)- said by the investigators to be possibly or probably related to Thyrogen in 5/6,

Swelling of metastases in sternum in 1 patient- not attributed to Thyrogen by the investigator,

Pain in 4/229 patients (2%) (in neck, hip, shoulder and thorax)- possibly/probably related to Thyrogen in 2,

Urticarial rash and itching at injection site- 1 patient each- possibly/probably related to Thyrogen,

decreased white blood cell count (wbc) in 2 patients- (see hematology parameters below)

Adverse Events during the WD Phase:

A total of 43/229 patients (19%) experienced AES during the WD phase. The most frequently reported AES were hypercholesterolemia and hypertriglyceridemia. Hypercholesterolemia was reported in 22/229 patients (10%) during the WD phase. In 2 of these 22 patients, the hypercholesterolemia was considered possibly related to Thyrogen. Note that increases in serum cholesterol may occur in patients when hypothyroid due to decreased excretion into the gut and a subsequent decrease in conversion to bile acids by the liver. Hypertriglyceridemia was reported as an adverse event in 10/229 patients (4%). None of these were attributed to Thyrogen.

The only adverse event occurring in ≥1% but <5% patients was an increase in creatinine in 4/229 patients (1.8%). The increase in creatinine during the hypothyroid phase is consistent with the well-established effect of the hypothyroid state on GFR.

Vital Signs:

There were no clinically significant changes in mean vital signs during the Thyrogen phase. Of interest, and not unexpected, was a decrease in mean pulse rate during the WD phase from a baseline of 76 bpm to 69 bpm.

Hematology Parameters:

There were no clinically significant changes in mean/median hemoglobin, hematocrit, or platelet counts during the Thyrogen or WD phases.

In one patient each during the Thyrogen and WD phases, there was a decrease in Hgb/Hct reported as AES (in 1, the Hgb decreased from 13.4 g/dl to 11.2 g/dl during Thyrogen; in the other, from 14.3 g/dl to 9.6 g/dl during WD).

In one patient each during the Thyrogen and WD phases, there was a decrease in wbc reported as AES (decrease from baseline of 4.4 x 10^3/uL to 3.7 x 10^3 /uL during the Thyrogen phase; in the other, from 4.5 x 10^3 to 2.5 x 10^3 during the WD phase).

Serum Chemistry Parameters:

Creatinine:

There was essentially no change from baseline in mean/median serum creatinine during the Thyrogen phase. Although there was an increase during the WD phase, mean/median values remained within normal limits (wnl):

- mean/median baseline creatinine- 1.0/0.9 mg/dl
" / " WD " - 1.2/1.2 "

There were 4 patients who experienced increases in creatinine levels during WD phase that were reported as AES. In all 4, baseline was normal (1.0-1.2 mg/dl) and increased to 1.6-1.8 mg/dl during WD (upper limit of normal- ULN- creatinine was 1.4 mg/dl). As stated above, the increase in creatinine levels observed during the hypothyroid phase is secondary to a decrease in GFR.

LFTs:

SGOT, LDH and alkaline phosphatase:

There was essentially no change from baseline in mean/median SGOT, LDH or alkaline phosphatase levels during the Thyrogen phase. Although mean/median SGOT and LDH levels increased from baseline during the WD phase, the levels remained well within normal limits.

The following were reported as AES:

2 patients during each of the Thyrogen and WD phases experienced elevations in SGOT from baseline that were reported as AES: Thyrogen phase (SGOT increased from 19 to 66 U/L in one patient and from 33 to 48 U/L in another)

WD phase (SGOT increased from 18 to 51 U/L in one patient and from 14 to 44 U/L in the other).

Cholesterol and Triglycerides:

There was essentially no change from baseline in mean/median serum cholesterol and triglyceride levels during the Thyrogen phase.

Mean/median cholesterol and triglycerides significantly increased from baseline during the WD phase:

cholesterol- mean/median baseline was 194/191 mg/dl
mean/median WD phase was 309/305
as noted above, this increase in the hypothyroid state is secondary to decreased excretion into the gut and a subsequent decrease in conversion to bile acids by the liver.

triglycerides- mean/median baseline was 137/116 mg/dl
mean/median WD phase was 212/175 mg/dl

Development of Thyrogen Antibodies:

Patients were evaluated for development of antibodies to Thyrogen at baseline and 3 to 6 weeks after Thyrogen administration using an ELISA developed by Genzyme. Normal human serum samples and a commercially available normal human serum pool were evaluated in the assay to establish the normal distribution range. Normal range was established as 3 SD from the mean observed in individual serum samples. None of the patients enrolled in study TSH95-0101 had levels above the normal range.

Compassionate Use Program:

There were 4 patients who experienced adverse events after compassionate Thyrogen use. These 4 cases will be discussed briefly here.

1. A 62 yr. old F with a history of follicular thyroid cancer and diffuse metastases in the brain, bone and spinal cord, received Thyrogen 0.9 mg IM x 2 days on a compassionate basis. 4 days previously, she had been hospitalized for seizures. 2 days after the second Thyrogen dose, the patient reported nausea, body/bone pain, right leg weakness and urinary incontinence and was treated with high dose dexamethasone. Concurrently, the patient received a tracer dose of ^{131}I. On the third day after the second Thyrogen dose, the patient experienced right hemiplegia followed a day later, by left ophthalmoplegia. A stat MRI revealed an increase in the size of the left parietal mass with progressive edema suspicious for bleeds of different ages. There was also evidence of possible hemorrhage within the clival mass. The following day, the patient received emergency radiotherapy to the brain and spine. A repeat MRI performed the following day confirmed the presence of a suspected hemorrhage. A later re-review of these MRI scans suggested that the increase in the parieto-occipital mass was due mainly to hemorrhage and edema rather than to an actual increase in tumor volume. It was difficult to determine if the clival mass had actually increased in size, but there was evidence of recent hemorrhage to the left of the clival mass with some increase in edema. As of the last report, the neurological symptoms had not fully resolved. Due to the temporal association, the treating physician considered this adverse event as possibly related to Thyrogen administration.

This same patient was hospitalized for fever, neutropenia and thrombocytopenia 3.5 weeks after receiving a second and final Thyrogen injection of 0.9 mg. A diagnosis of E. coli urosepsis was made. The patient was treated with antibiotics and granulocyte stimulating factor (G-CSF). However, 10 days later, she was readmitted to the hospital with fever and pancytopenia. She was diagnosed with pneumonia. A bone marrow biopsy revealed a hypoplastic marrow. The patient remains febrile in the hospital. The treating physician determined that these events were not related to Thyrogen administration.

2. A 55 yr. old M with widespread metastatic disease involving multiple bone sites, including the spine, experienced bone pain one day after the second Thyrogen dose of 0.9 mg. Two additional 0.9 mg Thyrogen doses were given 2 and 3 days later. On the day of the second dose, the patient experienced a right hemiparesis. The patient was treated with steroids and the neurologic symptoms resolved over the subsequent 7 days. The treating physician attributed the neurologic event to spinal cord compression and felt Thyrogen was the most likely etiology.

3. A 68 yr. old M with widespread metastatic disease to the spine, skull, ribs, long bones and brain, experienced acute pain and edema at the site of known metastases after a single 0.9 mg dose of Thyrogen. The increase in size of the rib metastasis was attributed to edema by the investigator; and an MRI of the brain revealed a frontal lobe lesion with adjacent edema. An MRI was not performed prior to Thyrogen administration, so no comparison