



**Table 2: Concordance of Positive Thyroid Scans Following THYROGEN Treatment with Scans Following Thyroid Hormone Withdrawal**

	Number of Scan Pairs by Disease Category	Concordance of scan pairs between THYROGEN scan and thyroid hormone withdrawal scan
<b>Study 1 (0.9 mg IM qd x2)</b>		
Positive for remnant or cancer in thyroid bed	48	81%
Positive for metastatic disease	15	73%
Total positive withdrawal scans <sup>a,b</sup>	63	79%
<b>Study 2 (0.9 mg IM qd x 2)</b>		
Positive for remnant or cancer in thyroid bed	35	86%
Positive for metastatic disease	9	67%
Total positive withdrawal scans <sup>a,b</sup>	44	82%

<sup>a</sup> Across both studies uptake was detected on the THYROGEN scan but not observed on the scan after thyroid hormone withdrawal in 5 patients with remnant or cancer in the thyroid bed.

<sup>b</sup> In the two clinical studies radioiodine scan results using thyroid hormone withdrawal were taken as the true clinical status of each patient and as the comparator for THYROGEN scans. Thyroid hormone withdrawal trace-positive scans were scored conservatively as positive with no allowance for false positives.

Across the two clinical studies, and scoring all false positives in favor of thyroid hormone withdrawal, the majority of positive scans using THYROGEN and thyroid hormone withdrawal were concordant. The THYROGEN scan failed to detect remnant and/or cancer localized to the thyroid bed in 17% (14/83) of patients in whom it was detected by a scan after thyroid hormone withdrawal. In addition, the THYROGEN scan failed to detect metastatic disease in 29% (7/24) of patients in whom it was detected by a scan after thyroid hormone withdrawal.

#### Thyroglobulin (Tg) Results

#### THYROGEN Tg Testing Alone and in Combination with Diagnostic Whole Body Scanning: Comparison with Results after Thyroid Hormone Withdrawal

In anti-Tg antibody negative patients with a thyroid remnant or cancer (as defined by a withdrawal Tg  $\geq$  2.5 ng/mL or a positive scan [after thyroid hormone withdrawal or after radioiodine therapy]), the THYROGEN Tg was positive ( $\geq$  2.5 ng/mL) in 69% (40/58) of patients after 2 doses of THYROGEN.

In these same patients, adding the whole body scan increased the detection rate of thyroid remnant or cancer to 84% (49/58) of patients after 2 doses of THYROGEN.

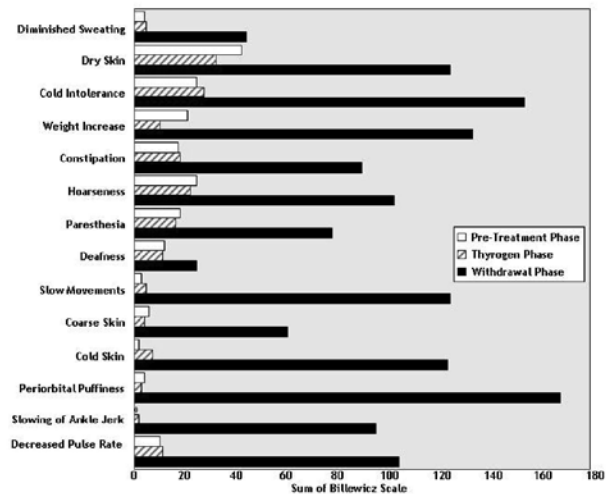
Among patients with metastatic disease confirmed by a post-treatment scan or by lymph node biopsy (35 patients), THYROGEN Tg was positive ( $\geq$  2.5 ng/mL) in all 35 patients, while Tg on thyroid hormone suppressive therapy was positive ( $\geq$  2.5 ng/mL) in 79% of these patients.

As with thyroid hormone withdrawal, the intra-patient reproducibility of THYROGEN testing with regard to both Tg stimulation and radioiodine imaging has not been studied.

#### Hypothyroid Signs and Symptoms

THYROGEN administration was not associated with the signs and symptoms of hypothyroidism that accompanied thyroid hormone withdrawal as measured by the Billewicz scale. Statistically significant worsening in all signs and symptoms were observed during the hypothyroid phase (p<0.01) (Figure 1).

**Figure 1: Hypothyroid Symptom Assessment Billewicz Scale Diagnostic Indication 0.9 mg THYROGEN® q 24 hours x 2 doses vs. Thyroid Hormone Withdrawal Phase**



#### 14.2 Clinical Trials of THYROGEN as an Adjunct to Radioiodine Therapy to Achieve Thyroid Remnant Ablation

A randomized prospective clinical trial compared the rates of thyroid remnant ablation achieved after preparation of patients with thyroid hormone withdrawal or THYROGEN. Patients (n = 63) with low-risk, well-differentiated thyroid cancer who underwent near-total thyroidectomy were made euthyroid after surgery by receiving thyroid hormone replacement and were subsequently randomized to a thyroid hormone withdrawal or THYROGEN. Patients in the THYROGEN group received THYROGEN 0.9 mg IM daily on 2 consecutive days and radioiodine 24 hours after the second dose of THYROGEN. Patients in the thyroid hormone withdrawal group had the thyroid replacement withheld until they became hypothyroid. Patients in both groups received 100 mCi <sup>131</sup>I  $\pm$  10% with the intent to ablate any thyroid remnant tissue. The primary endpoint of the study, was the rate of

successful ablation, and was assessed 8 months later by a THYROGEN-stimulated radioiodine scan. Patients were considered successfully ablated if there was no visible thyroid bed uptake on the scan, or if visible, if uptake was less than 0.1%. Table 3 summarizes the results of this evaluation.

**Table 3: Remnant Ablation in Clinical Trial of Patients with Well-Differentiated Thyroid Cancer**

Group <sup>a</sup>	Mean Age (Yr)	Gender (F:M)	Cancer Type (Pap:Fol)	Ablation Criterion (Measure at 8 Months)	
				Thyroid Bed Activity <0.1%	No Visible Thyroid Bed Activity <sup>b</sup>
Thyroid Hormone Withdrawal (N=28)	43	24:6	29:1	28/28 (100%)	24/28 (86%)
THYROGEN (N=32)	44	26:7	30:3	32/32 (100%)	24/32 (75%)

<sup>a</sup> 60 per protocol patients with interpretable scan data. 95% CI for difference in ablation rates THYROGEN minus Thyroid Hormone Withdrawal, = 7% to 27%.

<sup>b</sup> Interpretation by 2 of 3 reviewers. 95% CI for difference in ablation rates, THYROGEN minus Thyroid Hormone Withdrawal, = -31% to 9%. Abbreviations: fol = follicular, pap = papillary

The mean radiation dose to blood was 0.266 $\pm$ 0.061 mGy/MBq in the THYROGEN group and 0.395 $\pm$ 0.135 mGy/MBq in the thyroid hormone withdrawal group. Radioiodine residence time in remnant tissue was 0.9 $\pm$ 1.3 hours in the THYROGEN group and 1.4 $\pm$ 1.5 hours in the thyroid hormone withdrawal group. It is not known whether this difference in radiation exposure would convey a clinical benefit.

Patients who completed were followed up for a median duration of 3.7 years (range 3.4 to 4.4 years) following radioiodine ablation. Tg testing was also performed. The main objective of the follow-up study was to evaluate the status of thyroid remnant ablation by using THYROGEN-stimulated neck imaging. Of the fifty-one patients enrolled, forty eight patients received THYROGEN for remnant neck/whole body imaging and/or thyroglobulin testing. Only 43 patients had imaging. Patients were still considered to be successfully ablated if there was no visible thyroid bed uptake on the scan, or if visible, uptake was less than 0.1%. All patients from both original treatment groups who had scanning were found to still be ablated. Of 37 patients who were Tg-antibody negative, 16/17 (94%) of patients in the former thyroid hormone withdrawal group and 19/20 (95%) of patients in the former THYROGEN group maintained successful ablation measured as stimulated serum Tg levels of <2 ng/mL.

No patient had a definitive cancer recurrence during the 3.7 years of follow-up. Overall, 48/51 patients (94%) had no evidence of cancer recurrence, 1 patient had possible cancer recurrence (although it was not clear whether this patient had a true recurrence or persistent tumor from the regional disease noted at the start of the initial study), and 2 patients could not be assessed.

Two large prospective multi-center randomized studies compared THYROGEN to thyroid hormone withdrawal using two different doses of radioactive iodine in patients with differentiated thyroid cancer who had been thyroidectomized. In both studies, patients were randomized to 1 of 4 treatment groups: THYROGEN + 30 mCi <sup>131</sup>I, THYROGEN + 100 mCi <sup>131</sup>I, thyroid hormone withdrawal + 30 mCi <sup>131</sup>I, or thyroid hormone withdrawal + 100 mCi <sup>131</sup>I. Patients were assessed for efficacy (ablation success rates) at approximately 8 months.

The first study (Study A) randomized 438 patients (tumor stages T1-T3, Nx, NO and N1, M0). Ablation success was defined as radioiodine uptake of <0.1% in the thyroid bed and stimulated thyroglobulin levels of < 2.0 ng/mL.

The second study (Study B) randomized 752 patients with low-risk thyroid cancer (tumor stages pT1 < 1 cm and N1 or Nx, pT1 >1-2 cm and any N stage, or pT2 NO, all patients M0). Ablation success was defined by neck ultrasound and stimulated thyroglobulin of  $\leq$  1.0 ng/mL.

Results for both trials are summarized below.

**Table 4: Successful Remnant Ablation Rates in Study A**

	THYROGEN	Thyroid Hormone Withdrawal	Total
<b>Low-dose radioiodine</b>	91/108 (84.3%)	91/106 (85.8%)	182/214 (85.0%)
<b>High-dose radioiodine</b>	92/102 (90.2%)	92/105 (87.6%)	184/207 (88.9%)
<b>Total</b>	183/210 (87.1%)	183/211 (86.7%)	366/421 (86.9%)

95% CI of difference in ablation rate (low-dose minus high dose): -10.2% to 2.6%  
95% CI of difference in ablation rate (THYROGEN - Thyroid Hormone Withdrawal): -6.0% to 6.8%

**Table 5: Successful Remnant Ablation Rates in Study B**

	THYROGEN	Thyroid Hormone Withdrawal	Total
<b>Low-dose radioiodine</b>	160/177 (90.4%)	156/170 (91.8%)	316/347 (91.1%)
<b>High-dose radioiodine</b>	159/171 (93.0%)	156/166 (94.0%)	315/337 (93.5%)
<b>Total</b>	319/348 (91.6%)	312/336 (92.9%)	631/684 (92.3%)

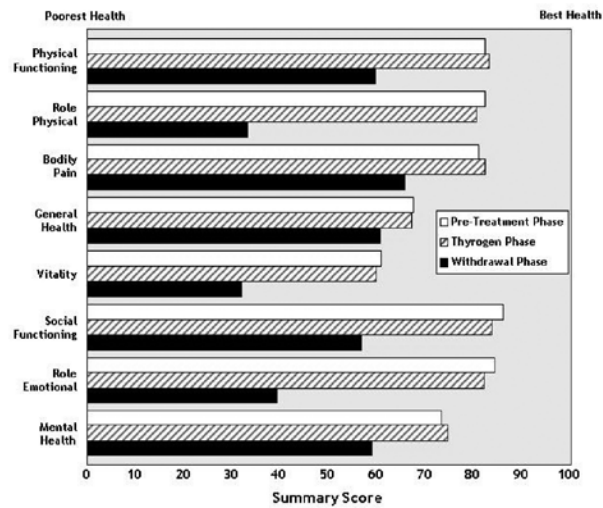
95% CI of difference in ablation rate (low-dose minus high dose): -5.8% to 0.9%  
95% CI of difference in ablation rate (THYROGEN minus Thyroid Hormone Withdrawal): -4.5% to 2.2%

#### 14.3 Quality of Life

Quality of Life (QOL) was measured during both the diagnostic study [see *Clinical Studies (14.1)*] and the ablation of thyroid remnant study [see *Clinical Studies (14.2)*] using the SF-36 Health Survey, a standardized, patient-administered instrument assessing QOL across eight domains measuring both physical and mental functioning. In the diagnostic study and in the remnant ablation study, following THYROGEN administration, little change from

baseline was observed in any of the eight QOL domains of the SF-36. Following thyroid hormone withdrawal in the diagnostic study, statistically significant negative changes were noted in all eight QOL domains of the SF-36. The difference between treatment groups was statistically significant (p<0.0001) for all eight QOL domains, favoring THYROGEN over thyroid hormone withdrawal (Figure 2). In the remnant ablation study, following thyroid hormone withdrawal, statistically significant negative changes were noted in five of the eight QOL domains (physical functioning, role physical, vitality, social functioning and mental health).

**Figure 2: SF-36 Health Survey Results Quality of Life Domains Diagnostic Indication**



#### 16 HOW SUPPLIED/STORAGE AND HANDLING

THYROGEN (thyrotropin alfa for injection) is supplied as a sterile, non-pyrogenic, lyophilized product. It is available either in a two-vial kit or a four-vial kit. The two-vial kit contains two 1.1 mg vials of THYROGEN. The four-vial kit contains two 1.1 mg vials of THYROGEN, as well as two 10 mL vials of Sterile Water for Injection, USP.

NDC 58468-1849-4 (4-vial kit)

NDC 58468-0030-2 (2-vial kit)

THYROGEN is for intramuscular injection to the buttock. The lyophilized powder should be reconstituted immediately prior to use with 1.2 mL of Sterile Water for Injection, USP [see *Dosage and Administration (2.2)*]. Each vial of THYROGEN and each vial of diluent, if provided, is intended for single use.

THYROGEN should be stored at 2-8°C (36-46°F).

If necessary, the reconstituted solution can be stored for up to 24 hours at a temperature between 2°C and 8°C, while avoiding microbial contamination.

Protect from light.

#### 17 PATIENT COUNSELING INFORMATION

##### Adverse Reactions

- Inform patients that the most common adverse events from clinical experience were nausea and headache.
- Advise patients to seek immediate medical attention should they experience severe symptoms.

##### Important Information

- Prior to THYROGEN administration, counsel patients to seek care immediately for any neurologic symptoms occurring after administration of the drug.
- Inform patients for whom THYROGEN induced hyperthyroidism could have serious consequences, hospitalization for administration of THYROGEN and post-administrative observation should be considered.

##### Dosing and Administration

- Patients should be instructed that THYROGEN is for intramuscular administration into the buttock only. THYROGEN should not be administered intravenously.
- Inform patients the treatment regimen is two doses of THYROGEN administered at a 24 hour interval.
- Encourage patients to remain hydrated prior to treatment with THYROGEN.

##### Schedule of Procedures

- Inform patients that if diagnostic scanning will be performed, radioiodine will be given 24 hours after the second injection of THYROGEN, and patients should return for the scan 48 hours after radioiodine administration.
- Inform patients that if serum Tg testing is performed, blood will be drawn 72 hours or later after the second injection of THYROGEN.
- Inform patients that if remnant ablation is performed radioiodine will be administered 24 hours after the second injection of THYROGEN.

THYROGEN is manufactured and distributed by:

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