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Product Name: THYROGEN
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SCIENTIFIC DISCUSSION

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1 Introduction

The MAH applied to include an indication for pre-therapeutic stimulation in post-thyroidectomy patients maintained on THST (e.g. Thyroxine) in the ablation of thyroid remnant tissue in combination with RAI. The intended posology for this new indication is the same as for the approved diagnostic indication. In support of this proposed new indication, the MAH has submitted a single randomised controlled study comparing the rates of thyroid remnant ablation achieved after patients were randomised to treatment with Thyrogen plus RAI *versus* hypothyroidism plus RAI. In addition, the MAH has submitted literature relevant to the use of Thyrogen as an adjunct to RAI therapy for the ablation of thyroid remnant tissue.

1.1 Rationale for the proposed change

Thyroid cancer is uncommon (2% of all cancers) and mainly affects female adults. The global incidence ranges from 0.5 to 10 cases per 100,000, with approximately 20,000 new cases diagnosed annually in Europe. Well-differentiated thyroid cancer accounts for 80-90% of all thyroid cancers. In general, patients respond well to therapy with a reported 10-year survival rate > 80%. Nonetheless, late recurrences, often decades after initial therapy, require life long follow up.

Primary treatment of well-differentiated thyroid cancer is (near)-total thyroidectomy followed by ablation of the remaining glandular tissue using a high dose of ^{131}I (RAI). Post-thyroidectomised patients lack the ability to produce thyroid hormone and require lifelong thyroxine replacement. High levels of circulating thyroid hormones inhibit TSH production. On the other hand, an elevated TSH level in the blood is essential for remnant ablation because TSH stimulates the uptake of ^{131}I into thyroid tissue and residual thyroid cancerous cells. Traditionally, stimulation of ^{131}I uptake has been achieved by withdrawing thyroxine replacement therapy, rendering the patient hypothyroid until levels of endogenous TSH are ≥ 25 mU/l. However, this hypothyroid state is often associated with a variety of symptoms (including depression, fatigue, cold intolerance, constipation, worsening hypertension, bradycardia and decreased myocardial contractility). Moreover, in some patients with heart disease, pulmonary disease, or other underlying medical illnesses, the hypothyroid state may aggravate these conditions. Therefore, alternative ^{131}I uptake-enhancing treatments avoiding hypothyroidism and associated morbidity are desirable.

Elevation of TSH in the blood using an exogenous source of TSH, such as Thyrogen, may be an attractive and similarly effective alternative. Clinical studies have confirmed that Thyrogen enhances ^{131}I uptake in thyroid tissue for whole body scanning (WBS) and stimulates a Tg response while patients remain euthyroid.

2 Clinical aspects

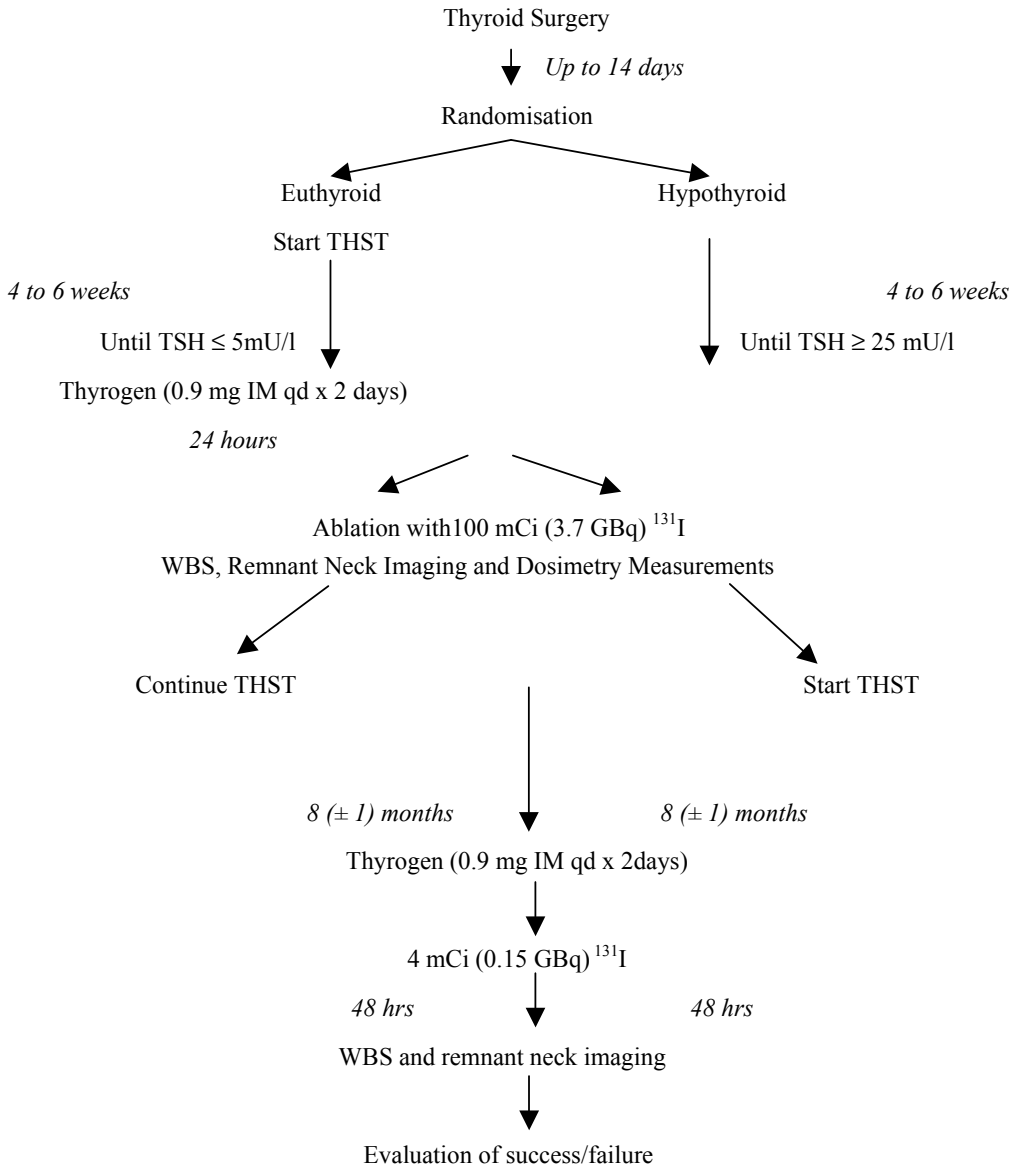
Analysis of data submitted

The *pivotal trial* (THYR-008-00) in this application was a randomised, controlled, open-label, multi-national study of thyroid remnant ablation comparing the safety and ablation rate following ^{131}I administration using Thyrogen vs. ^{131}I administration in the hypothyroid state.

Following total or near-total thyroidectomy patients were randomised within 14 days to one of the following 2 groups (see Figure 1):

- Euthyroid group: following randomisation patients immediately started on THST and TSH was measured after 4 weeks and, if necessary, additionally at 6 weeks. If TSH level was ≤ 5 mU/l, Thyrogen was administered at 0.9 mg IM qd x 2 days, and 24 hours following the second dose, an ablative activity of ^{131}I (100 mCi, 3.7 GBq) was administered orally.
- Hypothyroid group: Patients were not placed on THST until completion of the dosimetry assessments and were monitored for at least 4 weeks (and 1 and 2 weeks thereafter) until their TSH was ≥ 25 mU/l. Patients then received 100 mCi ^{131}I.

Figure 1: Flow Diagram of Ablation Study THYR-008-00



A wide range of ^{131}I doses (activity) (15 mCi – 200 mCi) is used to ablate thyroid remnants with the dose depending on the amount of residual tissue. A recent retrospective study showed that relatively low patient-specific doses (30-76 mCi) led to unsuccessful ablation in more than 40% cases. Successful ablation of 81% of 70 patients has been reported in the US using a dosimetric approach, as an alternative to empirical treatment, and the mean administered ^{131}I activity required to deliver 30,000 rads (cGy) to a typical remnant tissue was 87 mCi. Therefore, the consensus of experts recommended a routine dose of 100 mCi ^{131}I for this study.

Following ^{131}I ablation, whole body probe measurements and blood collections were conducted at 2 h, 6 h, 24 h, 48 h, 72 h to 96 h, and 96 h to 168 h (preferably 120 h) to obtain whole body ^{131}I activity data. Patients then underwent post-treatment WBS and remnant neck imaging at 48, 72 to 96 and at 96 to 168 hours (preferably 120 hours). In addition, the study allowed for the option to perform additional scans at 24 hours and between 144 and 168 hours. WBS was conducted using a dual-head scintillation camera that produced conjugate-view images of the whole body and of the neck. Following the 96 to 168 hour WBS and neck imaging, all patients received continuous THST. Three (±1) and 6 (±1) months after ablation, patients returned to the clinic for a safety check-up including TSH and Tg level determination. Eight (±1) months after ablation patients in both groups received Thyrogen (0.9 mg IM

qd x 2 days) while in the euthyroid state followed by 4 mCi ^{131}I. WBS and neck imaging were conducted 48 hours after the RAI administration. 3 independent readers to determine presence or absence of visible uptake in the thyroid bed evaluated the neck scan in a blinded manner. In cases where the majority of the readers determined that the RAI uptakes were detectable by eye and located in the thyroid bed, the percentage of ^{131}I uptake in the thyroid bed was determined. Basal and Thyrogen-stimulated serum Tg levels were obtained 72 hours after the second dose of Thyrogen.

The primary *objectives* were to demonstrate that the use of Thyrogen in euthyroid patients undergoing radioiodine remnant ablation results in a comparable ablation rate to patients in the hypothyroid state, and to document the safety profile of Thyrogen in this setting. Secondary objectives were to examine the patients' Quality of Life (QoL) and to compare the RAI uptake and retention into the thyroid bed and its clearance in the body.

The primary efficacy *endpoint* was successful thyroid remnant ablation as assessed by the 8 (±1) month follow-up scan and defined as a negative neck scan ("no visible uptake or, if visible uptake, less than 0.1% uptake in the thyroid bed"). In cases of scans with visible uptake, percentage uptake was quantified at the Dosimetry Coordination Centre. Thyroid remnant mass was estimated prior to the completion of each dosimetry assessment, as described in the Dosimetry Operational Manual. The proportion of the patients demonstrating treatment success was computed for each treatment group.

In addition to this primary endpoint, successful remnant ablation was also judged by a criterion suggested by the FDA of "no visible uptake in the thyroid bed", a secondary endpoint.

Adverse events (AEs) and serious adverse events (SAEs), laboratory findings (chemistry, haematology, and urinalysis), vital signs, changes in symptoms or physical findings, and development of antibodies to Thyrogen were assessed.

Secondary efficacy variables were individual and mean TSH and Tg levels, QoL determined using the SF-36 questionnaire and the Billewicz scale (a clinical symptom index for hypothyroidism consisting of 14 items) and RAI kinetics (activity-time curves, half-life (if appropriate), residence time, and area under activity-time curve) as determined by dosimetric calculations based on data from blood analysis and gamma camera counts. Stimulated serum Tg levels were also used to assess ablation success; a Tg cut-off level of 2 ng/ml was proposed as widely accepted and appropriate, although analyses using a cut-off level of 1 ng/ml were also performed as other experts have quoted this level. The SF-36 Health Status Survey and the Billewicz scale were completed at the time of randomisation, 2 weeks (±4 days) after randomisation, either 1 to 2 (± 2) days before ablation (Hypothyroid group) or just before Thyrogen administration before the ablation (Euthyroid group), and 1 month after ablation.

The following main *inclusion criteria* were applied: patients ≥18 years old with newly diagnosed differentiated papillary or follicular thyroid carcinoma, including papillaryfollicular variant, characterised as "T2, N0 or N1, and M0" or as "T1, N1, and M0" as defined by standard American Joint Committee on Cancer (AJCC) / International Union Against Cancer (UICC) criteria, with total or near-total thyroidectomy within 2 weeks prior to enrolment and previously untreated for thyroid malignancy (other than surgery), with normal complete blood count (CBC) and creatinine values, and standard precautions to avoid pregnancy.

The main *exclusion criteria* were:

- Hurthle cell carcinoma, anaplastic or medullary thyroid cancer, or lymphoma of the thyroid gland.
- Evidence of distant metastatic disease characterised as M1.
- Recent history (within the past 5 years) of concomitant malignancy, other than squamous or basal cell carcinoma of the skin or carcinoma *in situ* of the cervix.
- Concurrent major medical disorder (e.g. documented cardiac disease, advanced renal failure).
- Presence of non-thyroidal conditions known to affect ^{131}I uptake (e.g. congestive heart failure).
- Any iv water-soluble radiographic contrast within 4 weeks prior to ^{131}I administration.
- Intrathecal or cholecystographic iodinated contrast agent within 3 months prior to randomisation.

- Drugs that may affect thyroid or renal function (e.g. certain renal drugs, lithium, amiodarone, other iodine-containing medication, or corticosteroids).
- Long-acting thyroid hormone (i.e. levothyroxine) within 2 weeks prior to randomisation.

Patient radioiodine kinetics were assessed in the local laboratories in order to evaluate whole body and blood retention activity-time curves, clearance (hours), and cumulated activity. Urinary iodine samples were collected within 2 days prior to the ^{131}I administration (Hypothyroid group) or within 2 days prior to the Thyrogen administration (Euthyroid group), and at follow-up for both groups to rule out iodine excess, and measured by a designated central lab. TSH measurements were done at local laboratories using the same validated brand test kit. Serum samples for Tg measurements were frozen and sent to a designated central laboratory for evaluation. Tg levels were measured for all samples; the Tg antibody titre was measured from the sample collected at screening only. After the study was completed, data regarding the Tg antibody status of patients at 8 months became available.

Concerning *statistical methods and study design*, a 93% ablation rate for both groups was assumed based on recent published studies showing successful ablation rates ranging from 88% to 100%. The study size (at least 25 patients per group) was calculated so that by using the standard non-inferiority framework it would be possible to exclude a clinical difference of 20% in ablation rates. The probability that the 1-sided 97.5% confidence interval (CI) of the difference between the ablation rates in the 2 treatment groups would not include the clinically relevant difference was 79%. According to protocol, this study was intended to provide preliminary data and thus the study was not formally powered to assess treatment group differences; no formal hypothesis testing was planned on any parameter and outcomes were summarised and tabulated by treatment group for comparison. All efficacy analyses were to be performed on the Intent-to-Treat (ITT) population (all randomised patients). The primary efficacy analyses were also performed on the Per Protocol (PP) population (all ITT patients who satisfied the inclusion/exclusion criteria and did not exhibit major study protocol violations or deviations that would impact on the efficacy assessment).

Descriptive statistics of efficacy variables and 95% CIs for the difference between ablation rates were calculated for comparison of the 2 treatment groups with a predefined clinically relevant difference of 20%. No adjustment for covariates and no centre-stratified analysis was performed because the patient population was not large enough to produce meaningful results.

Results and Discussion

The MAH states that the study was conducted in accordance with GCP requirements.

Of 66 patients enrolled, 30 patients were randomised to the hypothyroid group, 33 to the euthyroid group and 3 were found to be ineligible. One patient in the hypothyroid group withdrew before the month 8 primary efficacy assessment due to an AE (lung metastases). All patients in the euthyroid group completed the study, although 1 patient was ineligible for inclusion in the PP population as they did not receive a second regular dose of Thyrogen before ablation.

Demographic and medical parameters and cancer types were similarly distributed between the 2 treatment groups. Tumour staging was not clearly different between the two groups except that slightly more patients in the hypothyroid group had a tumour extending the thyroid capsule (T4). All patients in the euthyroid and hypothyroid groups achieved the target TSH levels ($\leq$ 5 mU/l and $\geq$ 25 mU/l, respectively) within the pre-specified 6 weeks.

Efficacy

Since the ITT population and the PP population differed by only 2 patients, the decision was made to limit PP analysis to the scan and Tg level efficacy assessments.

The results of the WBS for the *primary* and FDA-recommended *endpoints* are shown below.

Table 1: Summary of Thyroid Remnant Ablation results at Month 8 Follow-Up (PP Population)

Uptake in Thyroid Bed	Hypothyroid (N=28)[1] n (%)	Euthyroid (N=32) n (%)	95% CI on Difference in Ablation Rates
No Visible Uptake or Uptake < 0.1%	28 (100)	32 (100)	N/A
Negative (No Visible Uptake)	24 (85.7)	24 (75.0)	(-30.5, 9.1)
Positive[2]	4 (14.3)	8 (25.0)	

[1] The scan from 1 patient (Patient 309) was not considered interpretable by 2 of the 3 readers.
[2] In every case where thyroid bed uptake was seen, the measured uptake was < 0.1% of the administered activity.

Using the pre-defined primary endpoint of "no visible uptake or, if visible, < 0.1% uptake" 100% of patients with interpretable scans had successful ablation. CIs cannot be formally calculated because there was 100% ablation in both groups. Using the endpoint recommended by the FDA of "no visible uptake in the thyroid bed" the results were higher in the hypothyroid group (85.7%) than the euthyroid group (75%) although when quantified, the amount of uptake was below the cut off of < 0.1% in each case. The sample size was not large enough for the 95% CI (-30.5%, 9.1%) to demonstrate non-inferiority of the euthyroid group vs. the hypothyroid group for the FDA-defined endpoint by excluding the predefined 20% difference in ablation rates.

Regarding *secondary endpoints*, the results of Thyrogen-stimulated serum Tg levels are shown below.

Table 2: Number of patients with serum Tg levels <2 ng/ml and <1 ng/ml at Month 8 (PP Population)

Group	**Serum Tg <2 ng/ml**
Hypothyroid (N = 28)[1]	18/21 (86%)
Euthyroid (N = 32)[1]	23/24 (96%)
95% CI for the difference in ablation rates	-6.85%, 27.09%
	Serum Tg <1 ng/ml
Hypothyroid (N = 28)[1]	18/21 (86%)
Euthyroid (N = 32)[1]	20/24 (83%)
95% CI for the difference in ablation rates	-23.5%, 18.7%

[1] *Patients with evaluable scans (at 8 months) and low anti-Tg antibody status at screening were included in the Tg analysis.*

Using the < 2 ng/ml cut-off level, the results indicate that remnant ablation was achieved in more euthyroid (96%) than hypothyroid patients (86%), and the 95% CI for the difference in ablation rates (-6.85%, 27.09%) excludes the relevant difference (20%) in the lower bound suggesting that the euthyroid group is non-inferior to the hypothyroid group. The results using a cut-off of < 1 ng/ml showed succesfull ablation was lower in the euthyroid group (83%) than the hypothyroid group (86%). The lower bound of the 95% CI (-23.5%, 18.7%) failed to exclude the predefined clinical difference of 20%, failing to demonstrate non-inferiority of the euthyroid group vs. the hypothyroid group.

Further to a request from CHMP, the MAH presented results of follow up scans on patients with Tg concentrations above either cut-off level. Out of 9 patients with detectable stimulated Tg at 8 months (5 had > 2ng/ml) only one had a positive WBS. On the other hand, of 15 patients with detectable thyroid bed uptake only 2 (13%) had elevated stimulated Tg, consistent with the increasing physician reliance on Tg testing in the absence of anti Tg antibodies.

Patients in both treatment groups started with high mean TSH levels, as they were not on THST at time of surgery. In the hypothyroid group, the level rose to 82.9mU/l by week 4 and all reached the

required 25mU/l within the protocol-specified time. At 8 months post-ablation the mean TSH level was 0.2 mU/l, indicating good THST compliance. In the euthyroid group, the mean TSH level was low at week 4 (1.1mU/l) due to THST. All patients reached the required ≤ 5mU/l within the specified time. At 8 months the mean TSH level was unexpectedly high (3.3mU/l) due to 1 patient (96mU/l) who had not taken TSHT properly.

Regarding *radioiodine kinetics*, the fraction of administered ^{131}I activity found in the whole body at different time points showed a somewhat faster decrease in the euthyroid group than the hypothyroid group (e.g. the mean fraction of administered activity at 48 hours was 6.5% and 12.6 %, respectively). Consequently, the mean residence time (MRT) in the whole body was higher in the hypothyroid (24.0 ± 7.63 h) than the euthyroid group (17.3 ± 3.89 h).

A faster decrease in the mean fraction of administered activity at 48 hours was also seen in the blood of euthyroid (0.8%) *vs.* hypothyroid group (1.8%). MRT in the blood was also lower in the euthyroid group (2.3 ± 0.73 h *vs.* 3.5 ± 1.63h). The mean dose to blood per unit (MBq) of administered activity, a surrogate measure for dose-limiting bone marrow dose, was lower in the euthyroid (0.266 ± 0.0613 mGy/MBq) than the hypothyroid group (0.395 ± 0.1345 mGy/MBq), assuming 0.2-mm radius blood vessels and calculated from the fit to data.

The fraction of administered activity, MRT and mean percentage uptake in remnant tissue were also slightly higher in the hypothyroid group at different time points, as shown in the table below.

Table 3: Summary of ^{131}I Kinetics in Remnant Tissue (ITT Population)

Parameter	Summary Statistic	Hypothyroid (N= 30)	Euthyroid (N= 33)
Residence time in remnant tissue (hour)	n	29	33
	Mean (SD)	1.4 (1.51)	0.9 (1.27)
	Median	0.8	0.4
	Range	0.0-5.9	0.0-6.6
Effective half-life in the remnant (hour)	n	29	33
	Mean (SD)	48.0 (52.64)	67.6 (48.85)
	Median	26.9	51.1
	Range	16.0-192.5	17.3-192.5
Uptake in remnant tissue (%)	n	29	33
	Mean (SD)	0.9 (1.05)	0.5 (0.70)
	Median	0.5	0.3
	Range	0.0-4.3	0.0-3.4
Area of remnant tissue in 48-h neck image (cm^2)	n	30	33
	Mean (SD)	18.8 (17.03)	16.2 (10.42)
	Median	18.9	14.0
	Range	-1.1-84.3	-0.7-48.8

Although these results seem to support the hypothesis of reduced RAI exposure for euthyroid patients, the study was not powered to find differences in ^{131}I kinetics in remnant tissue between the 2 groups.

The mean urinary iodine (µg/dl) was higher, although below the threshold considered critical for efficient RAI uptake, in the Euthyroid group than in the hypothyroid group. A *post-hoc* analysis showed that the differences were not statistically significant. The mean creatinine clearance was higher in the euthyroid (143.5 ± 92.4 ml/min) than hypothyroid group (92.4 ± 46.2 ml/min), although individual patient creatinine clearance values (except for 1 patient) were determined not to be clinically significant.

Regarding QoL measures, the SF-36 scale showed statistically significant reductions in 5 of the 8 domains for the hypothyroid group at week 4: Physical Functioning, Role Physical, Vitality, Social Functioning, and Mental Health.

Table 4: Mean Change in SF-36 Scores from Baseline to Week 4 (Safety Population)

SF-36 Domain	Hypothyroid mean (SD) (N=30)	Euthyroid mean (SD) (N=33)	p-value[1]
Physical Functioning	-13.2 (28.90)	2.1 (17.60)	0.016*
Role Physical	-14.2 (45.81)	14.1 (45.76)	0.018*
Bodily Pain	0.9 (30.85)	9.8 (32.93)	0.277
General Health	-6.3 (13.52)	-1.8 (18.46)	0.279
Vitality	-19.3 (21.62)	8.4 (16.87)	<0.0001*
Social Functioning	-14.2 (25.37)	11.7 (22.44)	<0.0001*
Role Emotional	-18.9 (57.86)	9.4 (55.02)	0.053
Mental Health	-5.2 (19.83)	9.3 (14.09)	0.002*

[1] Hypothesis testing used 2-sided t-test.

*Indicates statistical significance ($p<0.05$)

Using the Billewicz scale the hypothyroid group reported more events of cold intolerance (50.0% vs. 21.2%), weight increase (60.0% vs. 21.2%), constipation (43.3% vs. 3.0%), slow movements (50.0% vs. 12.1%), cold skin (46.7% vs. 12.1%), and periorbital puffiness (50.0% vs. 0%) during the 4-week period preceding ablation compared to the euthyroid group. Mean total scores returned to the level seen in the euthyroid group 1 month after ablation, when Hypothyroid patients were again on THST.

Supportive studies: Published literature

Four studies and a report of the use of Thyrogen as an adjunct to ^{131}I remnant ablation have been published since 2001. No serious safety problems have been identified in these studies.

	No. of patients with well differentiated cancer	Mean ablative ^{131}I dose	Definition of successful ablation	rhTSH stim Tg levels
Robbins 2001[1]	9 Thyrogen	110.3mCi (30-250)	No uptake in any patient 9/9 100%	
Robbins 2002[2]	87 THW- 42 Thyrogen -45	THW - 128.9 Thyrogen- 110.4mCi	81% THW vs. 84.4% Thyrogen	Cut-off 2ng/ml THW 15/42 35% vs. rhTSH 10/44 22%
Barbaro 2003[3]	24 -THW 16- rhTSH stopped T4 x4ds	30mCi	THW 75% vs. Thyrogen 81%	
Pacini 2002[4]	50- THW 42- THW+rhTSH 70-euthyroid on T4 +rhTSH	30mCi	THW- 84% THW+rhTSH -78.5% euthyroid on T4 +rhTSH - 54%	
Berg 2002[5]	3 Thyrogen	108mCi		

[1] Robbins RJ et al. *Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin.* Thyroid. 2001; 11:865-869.

[2] Robbins RJ et al. *A retrospective review of the effectiveness of recombinant human TSH as a preparation for radioiodine thyroid remnant ablation*. J Nucl Med, 43:1482-1488, 2002.

[3] Barbaro D et al. *Radioiodine Treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: effectiveness for postsurgical remnant ablation and possible role of iodine content in L-thyroxine in the outcome of ablation.* J Clin Endocrinol Metab 88:4110-4115, 2003.

[4] Pacini F et al. *Ablation of thyroid residues with 30 mCi ^{131}I: a comparison in thyroid cancer patients prepared with recombinant human TSH or thyroid hormone withdrawal*. J Clin Endocrinol Metab, 87:4063-4068, 2002.

[5] Berg G et al. *Radioiodine ablation and therapy in differentiated thyroid cancer under stimulation with recombinant human thyroid-stimulating hormone*. J Endocrinol Invest 25:44-52, 2002.

Two studies were performed at the Memorial Sloan-Kettering Cancer Center (Robbins 2001; Robbins 2002). In the first study, 10 patients (5M, 5F, mean age 47.5 years) were maintained on thyroxine and given Thyrogen (0.9 mg IM qd for 2 days) followed by ^{131}I (mean dose 110.3 mCi). Nine patients had papillary thyroid cancer (four with positive cervical nodes) and one poorly differentiated thyroid cancer. Follow-up diagnostic scans (DxWBS) were obtained 5-13 months later using a scanning dose of 5 mCi. No visible uptake was present in the thyroid bed in any patient.

The second paper (Robbins 2002) describes a retrospective review of clinical practice and patient outcomes in 87 patients (mean age 45 years) with differentiated thyroid cancer who underwent thyroid remnant ablation over a 2-year period. The study was not randomised but the MAH states the authors felt the assignment of patients to a regimen of Thyrogen (n = 45) vs. thyroxine withdrawal (n = 42) was relatively unbiased. The mean ablative dose of ^{131}I was 110.4 mCi for Thyrogen and 128.9 for THW, respectively. At follow-up diagnostic scanning after ablation (mean 11 months), 84% prepared using Thyrogen and 81% prepared by THW showed no visible uptake in the thyroid bed. The median Thyrogen-stimulated serum Tg levels at follow-up were 0.5 ng/ml (range 0.3-4980 ng/ml) in the Thyrogen group and 0.65 ng/ml (range 0.3-5000 ng/ml) in the THW group (p=0.48). Ten of 44 (22%) patients in Thyrogen group vs.15 of 42 (35%) in the THW group were above the Tg cut off of <2ng/ml. Robins concluded that the two methods of preparation for ^{131}I ablation gave similar results.

Comparable findings have been recently published (*Barbaro et al*, 2003). Sixteen consecutively enrolled patients (10 F, 6 M; age range 22 – 71 years) with well-differentiated thyroid cancer were assigned to receive Thyrogen (0.9 mg IM qd on 2 days) while euthyroid. Thyroxine was omitted on 4 days of the regimen (from the day before first Thyrogen injection until the day after ^{131}I administration) in an attempt to lower any theoretical interference of the iodine content of thyroxine with the radioiodine therapy. Another 24 consecutively enrolled patients (18 F, 6 M; age range 24 – 69 years) were assigned to THW. All received 30 mCi ^{131}I and DxWBS assessed the efficacy of ablation after 1 year. A non-statistically significantly higher rate of successful ablation was achieved by Thyrogen stimulation compared with the hypothyroid state (81% versus 75%).

In contrast, *Pacini et al.* (2002) reported a lower rate of successful ablation for patients with differentiated thyroid cancer prepared with Thyrogen compared to THW. In this study 30 mCi ^{131}I was administered 48 hours after the last injection of Thyrogen, rather than 24 hours as recommended in the SPC. The pre-ablation regimens used were THW (n = 50), THW + Thyrogen (n = 42), and euthyroidism + Thyrogen (n = 70). Patients had similar baseline characteristics, none had known distant metastases and they were consecutively enrolled into the 3 groups. Diagnostic scanning was performed at 6-10 months. Successful ablation was defined as "no visible uptake of radioiodine in the thyroid bed". The rates of successful ablation were 84%, 79%, and 54%, respectively. The MAH suggests that use of a suboptimal timing of the ^{131}I schedule with respect to Thyrogen administration might explain the less favourable outcome compared with the other studies, as mean peak serum TSH concentrations are reached 10-24 hrs after the last administration of Thyrogen.

There is a further publication (*Berg 2002*) of 11 patients with well-differentiated thyroid cancer treated with Thyrogen (0.9 mg IM x 2 doses) as an adjunct to radioiodine therapy (108 mCi) in elderly or frail patients. Ablation of a thyroid remnant was the intent in only 3 of the patients (aged 78, 75 and 56 years). All 3 patients were thought to have had their thyroid remnants fully ablated as judged by <0.1% uptake in the thyroid bed and low serum Tg levels.

Safety

The safety population for study THYR-008-00 included all 63 randomised patients.

Adverse events (AE)

The *Pre-treatment period* is defined as the time from randomisation to ablation (hypothyroid group) or to Thyrogen administration (euthyroid group), which for both groups could last from 4-6 weeks. During this period, 13 (39.4 %) euthyroid patients experienced 36 AEs, of which asthenia and fatigue was the most common (3 patients each). One patient experienced a SAE (worsening infection of the first finger) not related to study medication and fully recovered. In the hypothyroid group, 12 (40.0%) patients experienced 30 AEs, of which headache and nausea were the most common (3 patients each).

Treatment-emergent AEs are defined as events occurring from time of ablation (hypothyroid group) or Thyrogen treatment (euthyroid group) until follow-up at month 8 or last observation. The percentages of patients in the hypothyroid and euthyroid groups experiencing treatment-emergent AEs (78.8% vs. 73.3%), SAEs (3.0 vs. 6.7), severe AEs (6.1 vs. 13.3) and (at least possibly) treatment-related AEs (24.2 vs. 26.7) were similar. The most frequent AEs in the Euthyroid group were fatigue, insomnia, rhinitis, anxiety, pharyngitis, nausea, paraesthesia, and skeletal pain, pain, back pain, malaise, coughing, headache, sweating increased, and urinary tract infection. In the Hypothyroid group, fatigue, nausea, lab test abnormal, insomnia, skeletal pain, and pain were the most frequent AEs.
No deaths occurred during this study.

The *Ablation Period* was defined as the time period from time of ablation (Hypothyroid) or the time of Thyrogen treatment (Euthyroid) up to 7 days after ablation, after which both groups were treated identically. As shown in the Table below, 13 (43.4%) Hypothyroid patients and 15 (45.5%) patients in the Euthyroid group experienced at least 1 AE.

Table 12-3 Treatment-emergent Adverse Events During the Ablation Period in ≥ 2 Patients Per Treatment Group (Safety Population)

Body System Preferred Term	**Hypothyroid (N=30) n (%)**	**Euthyroid (N=33) n (%)**
Any Adverse Events	13 (43.3)	15 (45.5)
Psychiatric Disorders	3 (10.0)	5 (15.2)
Insomnia	1 (3.3)	2 (6.1)
Anxiety	0	2 (6.1)
Gastro-Intestinal System Disorders	4 (13.3)	4 (12.1)
Nausea	4 (13.3)	2 (6.1)
Diarrhoea	0	2 (6.1)
Centr & Periph Nervous System Disorders	2 (6.7)	5 (15.2)
Hypoaesthesia	0	2 (6.1)
Paraesthesia	0	2 (6.1)
Body As A Whole - General Disorders	3 (10.0)	4 (12.1)
Fatigue	1 (3.3)	2 (6.1)
Skin And Appendages Disorders	1 (3.3)	3 (9.1)
Sweating Increased	1 (3.3)	2 (6.1)
Special Senses Other, Disorders	2 (6.7)	2 (6.1)
Taste Loss	1 (3.3)	2 (6.1)

Reference: Table 14.3.2-5
Note: A patient experiencing more than one adverse event within a body system or preferred term is counted once within that body system or preferred term.
Note: Body System data reflect all patients who experienced AEs, while the Preferred Term data reflect only those AEs with a frequency of ≥2 patients. Therefore, the sum of Preferred Terms may not equal the total for their Body System.

The AEs of 8 patients in each group were considered at least possibly related to use of the study medication. There were 23 *treatment-related AEs* in the Euthyroid group and 14 in the hypothyroid group. The most frequently reported treatment-related AEs were nausea (4 patients) and fatigue and taste loss (2 patients each) in the Euthyroid group, and fatigue (3 patients) and nausea and skeletal pain (2 patients each) in the hypothyroid group. One Euthyroid patient experienced 2 episodes of nausea and 2 episodes of taste loss. All other patients in both treatment groups experienced no more than 1 occurrence of each related AE.

Regarding *discontinuations* due to AEs, 1 patient (Hypothyroid group) withdrew before the primary efficacy assessment (Month 8) due to disease progression NOS, reported as severe and unrelated.

Mean values for *blood chemistry* and haematology were similar in both treatment groups. One hypothyroid patient had elevated baseline AST and ALT values, which increased at month 8. This was considered unrelated to study drug. Another patient (hypothyroid group) had a normal baseline creatinine, which increased at week 4 and returned to within the normal range at month 8. This was also considered unrelated to study drug.

There were no indications during the study that warranted testing for anti-TSH *antibodies*. Antibodies to Tg were tested at screening since they can interfere with proper measurement of serum Tg levels. The protocol specified that patients who were "positive for antibodies" should be excluded from analyses related to Tg levels. However, nearly every patient had detectable trace titres (or higher) of antibody at the conclusion of the study. It was necessary to refine the definition of "positive for antibodies", which was arbitrarily set at a limit of 50 U/ml. Eight patients (euthyroid group) and seven (hypothyroid group) had values > 50 U/ml (most were substantially higher); all 15 patients were excluded from the Thyrogen-stimulated Tg analyses.

Discussion

The study design is acceptable; the treatments and their assessment are scientifically sound and in accordance with current guidelines.

Efficacy

The application is based on a single pivotal study. The CPMP Points to Consider (PtC) on Applications with One Pivotal study (CPMP/EWP/2330/99) states that the extent of confirmatory phase III data needed depends upon what is established for the product by earlier development phases and what is known of related products. The pharmacological rationale of Thyrogen therapy is known, and the safety and tolerability have been previously evaluated in studies supporting the original approval. As regards the dose response, the rationale for the choice of dose in this pre-remnant ablation population has not been provided.

Study THYR-008-00 meets the fundamental requirements of phase III documentation in terms of internal validity (i.e. no indication of potential bias), lack of individual centre effect, clinical relevance and data quality. However, some weaknesses have been noted with respect to the CHMP PtC, regarding internal consistency (different endpoints did not show similar findings), external validity (small study population i.e. 63 patients, 33 of whom received Thyrogen, only patients who received an ablative dose of 100mCi were studied.) and the degree of statistical significance (the sample size was too small and the 95% CI of the FDA-defined endpoint and the Tg level cut-off of < 1 ng/ml failed to demonstrate non-inferiority of the euthyroid group).

The success of remnant ablation is judged using the results of both WBS results and Tg measurements. According to the predefined primary endpoint and serum Tg levels (< 2 ng/ml), the rates of successful ablation were the same (WBS) or higher (Tg levels) in the euthyroid group compared to the hypothyroid group. However, the results for the FDA-defined endpoint, a commonly used criterion to define successful remnant ablation, and the lower Tg cut off level (< 1 ng/ml) were lower in the euthyroid group and failed to demonstrate non-inferiority of the euthyroid group with respect to the hypothyroid group.

The MAH argues that there is no consensus on the clinical significance of <0.1% visible uptake on WBS in low risk patients, as an uptake in the thyroid bed of less than 0.1% (or even 0.5%) at 48 hours is unlikely to represent residual cancer if the Tg levels are low. Study THYR-008-00 showed very poor correlation between positive thyroid bed uptake and the Tg levels, as most patients who had detectable thyroid bed uptake did not have a rise in Tg. One of the published studies cited concluded that undetectable serum Tg levels, defined as < 3ng/ml, is highly predictive of complete and persistent remission and that persistent areas of visible trace uptake were of clinical significance in only 0.6% (2) patients. Following consultation with Radiotherapy Experts this view is accepted by the CHMP as in practice, if patients have residual (<0.1%) visible uptake on WBS, physicians increasingly rely upon the results of the stimulated Tg level, in the absence of anti Tg antibodies, to determine if significant thyroid tissue remains and further therapy is necessary.

Although there is no final answer on whether the 1 or 2 ng/ml cut-off is clinically more relevant, the widely accepted value of < 2 ng/ml is considered acceptable by CHMP taking into account that well-differentiated thyroid cancer is a very uncommon cancer with only approximately 20,000 new cases diagnosed annually in Europe and larger studies may not be feasible. Therefore by the 2 pre-defined criteria "no visible uptake or, if visible, <0.1% uptake" on WBS and Thyrogen-stimulated serum Tg level of < 2 ng/ml comparable thyroid remnant ablation rates were found in patients prepared for post-operative ^{131}I therapy by thyroxine withdrawal or by Thyrogen.

Analyses of radioiodine kinetics showed the MRT was shorter in the euthyroid than the hypothyroid group in both whole body and remnant tissue. The MAH states that these results seem to support the hypothesis of reduced activity exposure for euthyroid patients. However, the study was not powered for statistical analyses of dosimetry parameters or to find differences in ^{131}I kinetics in remnant tissue between the 2 groups. Thus, the MAH's suggestion of a theoretical benefit in relation to a lower long-term risk risk of secondary malignancies due to reduced radiation exposure in the euthyroid group is speculative, as no data on long-term risk with Thyrogen have been provided.

Quality of life was significantly reduced in the hypothyroid group up to 1 month (SF-36) and more events of cold intolerance; weight increase, constipation, slow movements, cold skin, and periorbital puffiness were reported (Billewicz scale). From the clinical perspective this is important, as patients do not tolerate a period of hypothyroidism well and some are unfit to do so.

Further efficacy information comes from 4 published studies, 3 retrospective and 1 prospective, in which a total of 185 patients received Thyrogen as adjunct to ^{131}I remnant ablation. Fifty-seven received > 100 mCi ^{131}I and 128 received 30 mCi ^{131}I. The results of the latter group are inferior. In this respect, the lower uptake and MRT time of ^{131}I observed in remnant tissue in the pivotal study may suggest that low doses of ^{131}I could be less effective in Thyrogen-prepared compared to hypothyroid patients. Considering that all patients in study THRY-008-00 received an ablative dose of 100mCi, efficacy with Thyrogen at lower doses of ^{131}I has not been established. This has been reflected in sections 4.1 and 5.1 of the SPC.

Finally, study THYR-008-00 included only low risk patients. This has been reflected in section 4.1 and 5.1 of the SPC.

Safety
Treatment with Thyrogen was well tolerated and no safety concerns were identified. This was to be expected since the dose and dosing schedule are identical to that approved for diagnostic use. The incidence of AEs was similar in both groups and hence Thyrogen does not appear to be associated with a higher risk of undesirable events compared with remnant ablation in a hypothyroid state.

3. Conclusions and Benefit/Risk Assessment

Thyrogen was originally approved on the basis of a full dossier submitted to support its diagnostic use. The rationale for the proposed use in pre-therapeutic stimulation is the same. Globally, more than 100,000 patients have received Thyrogen for diagnostic use and the reported safety profile indicates that Thyrogen is well tolerated. Thyrogen is not associated with a higher risk of undesirable events compared with remnant ablation in a hypothyroid state.

Despite certain statistical limitations due to the small sample size, the results of study THRY-008-00 are clinically relevant in the intended population, at the intended dose. The applicant has shown that Thyrogen is effective for pre-therapeutic stimulation in post-thyroidectomy patients maintained on THST in the ablation of thyroid remnant tissue (in combination) with radioactive iodine > 100mCi. The rates of successful remnant ablation as determined by "no visible uptake or, if visible, <0.1% uptake" on WBS and Thyrogen-stimulated Tg level < 2 ng/ml were comparable to thyroid hormone withdrawal. Moreover, the avoidance of a period of hypothyroidism of 4-6 weeks and its associated morbidity in preparation for ablation therapy is a clear advantage for the affected patients. In addition, the use of Thyrogen preparation improves QoL and facilitates treatment planning.