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# ASSESSMENT REPORT FOR THYROGEN

**International non-proprietary name/Common name: thyrotropin alfa**

Procedure No. **EMEA/H/C/220/II/38**

**Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

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## 1. Introduction

Thyrotropin alfa (recombinant human thyroid stimulating hormone) is a heterodimeric glycoprotein produced by recombinant DNA technology. It is comprised of two non-covalently linked subunits. The cDNAs encode for an alpha subunit of 92 amino acid residues containing two N-linked glycosylation sites, and a beta subunit of 118 residues containing one N-linked glycosylation site. It has comparable biochemical properties to natural human Thyroid Stimulating Hormone (TSH). Binding of thyrotropin alfa to TSH receptors on thyroid epithelial cells stimulates iodine uptake and organification, and synthesis and release of thyroglobulin, triiodothyronine ($T_3$) and thyroxine ($T_4$).

Thyrogen (thyrotropin alfa) is indicated for use with serum thyroglobulin (Tg) testing with or without radioiodine imaging for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy (THST).
Low risk patients with well-differentiated thyroid carcinoma who have undetectable serum Tg levels on THST and no rh TSH-stimulated increase of Tg levels may be followed-up by assaying rh TSH-stimulated Tg levels.

Thyrogen (thyrotropin alfa) is also indicated for pre-therapeutic stimulation in low risk (see section 5.1) post-thyroidectomy patients maintained on hormone suppression therapy (THST) for the ablation of thyroid remnant tissue (in combination) with 100 mCi (3.7 GBq) radioactive iodine ($^{131}$I).

In this type II variation application, the Marketing Authorisation Holder (MAH) proposed to change the indication wording of the use of Thyrogen for ablation of thyroid remnant tissue further to the result of the follow-up clinical study THYR01605 and of published investigator-sponsored studies.

The MAH proposed to extend the ablation of thyroid tissue remnants indication of Thyrogen from low risk patients to patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastatic thyroid cancer. As a consequence, changes were made to sections 4.1, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics (SPC). Annex II has been updated to include the agreed version of the RMP and the change to the PSUR cycle. Minor editorial changes were made to the Labelling. The Package Leaflet was updated in accordance with the SPC and to update the list of local representatives.

## 2. Clinical aspects

### 2.1 Rationale for the proposed changes

Radioiodine thyroid remnant ablation can be defined as the post-surgical therapeutic administration of $^{131}$I to patients with differentiated thyroid cancer (DTC) with the primary goal of eliminating residual thyroid tissue following thyroidectomy. The procedure's potential benefits include:

- improving the sensitivity and specificity of follow-up testing for DTC persistence or recurrence, i.e., of serum Tg testing, diagnostic whole body scan (dxWBS), or both
- permitting sensitive "post-therapy" whole body scan (WBS) that may reveal previously occult metastases
- eradicating any microscopic tumour deposits, which may reduce both the frequency of regional recurrences and overall mortality in patients.

According to the recently-published European Association of Nuclear Medicine (EANM) guidelines on radioiodine therapy (Luster, 2008; *Eur J Nucl Med Mol Imaging*), ablation currently is considered a standard component of the primary treatment of DTC patients without distant metastases (except for individuals with unifocal papillary carcinoma ≤1 cm in diameter who lack evidence of metastasis, thyroid capsule invasion, history of radiation exposure, or unfavourable DTC histology).

Because TSH stimulation greatly enhances the $^{131}$I uptake into thyroid tissue, the low serum TSH levels that normally occur during thyroid hormone therapy result in low radioiodine uptake. An elevated TSH level in the blood is essential for efficient thyroid remnant ablation.

In the past, TSH elevation has been achieved by weeks-long Thyroid hormone withdrawal or withholding (THW; delaying starting thyroid hormone therapy after thyroidectomy or i.e., temporarily stopping thyroid hormone therapy begun after thyroidectomy). THW, however, renders patients clinically hypothyroid, a state that frequently induces morbidity that can have important negative effects on patients' ability to work, study and pursue leisure activities, on their quality-of-life (QOL) and on their concomitant psychological, cardiac, cerebrovascular, lipidaemic, renal and other disorders.

Thyrogen (thyrotropin alfa; recombinant human thyroid-stimulating hormone) was developed to provide TSH elevation to stimulate radioiodine uptake, Tg secretion, or both while sparing patients THW and consequent hypothyroid morbidity and QOL impairment. The indication for the ablation of thyroid remnant was approved in the EU on 23 February 2005 (EMEA/H/C/220/II/18). This approval was based primarily on a Genzyme-sponsored, prospective, randomised, controlled, multicentre, multinational open-label, pivotal Good Clinical Practice (GCP) study THYR-008-00.

Since then, THYR01605, a Genzyme-sponsored, prospective, multicentre, multinational follow-up study to THYR-008-00, examining the persistence of ablation and the DTC-related outcome since the end of THYR-008-00, has been completed.

Moreover, a total of 12 investigator-initiated studies of Thyrogen-assisted ablation have now been published. The nature of the data provided in the literature is not detailed enough to support a formal meta-analysis across studies, and a meta-analysis was thus not presented by the MAH. Nevertheless, the major endpoints of the various studies have been compared and these study results were discussed in this application.

Collectively, THYR01605 and the investigator-initiated studies have expanded the reported patient population given Thyrogen-assisted ablation, including patients with advanced local (T3 or T4) disease or nodal involvement (N1), expanded the range of ablative activities used with Thyrogen and extended the duration of follow-up post Thyrogen-assisted ablation (to as long as ~4 years).

In addition, new European DTC management guidelines have also been published pertaining to thyroid remnant ablation (Pacini, 2006, *Eur J Endocrinol*; Luster, 2008, *Eur J Nucl Med Mol Imaging*), reflecting changes in clinical practice with respect to the procedure.

As a result of the experience from THYR01605 and the investigator-initiated studies, and due to these practice changes, the MAH applied to change the wording of the ablation indication with respect to:

- Broadening the therapeutic indication by removal of the term 'low risk', i.e. T3, T4 and N1 patients without distant metastases belong to the patient population for Thyrogen-assisted ablation;
- Deleting the radioactive iodine activity to be used (100mCi), and thus expanding administration of Thyrogen from patients in whom 100 mCi radioactive iodine is used to patients in whom any radioiodine activity, including $^{131}$I activities lower than 100 mCi, is administered.

## 2.1 Clinical efficacy

- ***Genzyme-sponsored studies: Ablation study THYR-008-00***

The current remnant ablation indication of Thyrogen was based largely on the prospective, randomised, controlled, open-label, multicentre pilot study THYR-008-00. In this study, either Thyrogen or THW was used for preparing patients for thyroid remnant ablation and safety and ablation rates following $^{131}$I administration in the two groups were compared.

The study involved 63 patients with newly diagnosed T0-2 or T4, N0-1, M0 or MX DTC (a few patients were classified as MX, distant metastasis status unknown, pending results of the post-ablation WBS). The patients had recently undergone near-total or total thyroidectomy. According to protocol, no formal hypothesis testing was planned.

The primary efficacy endpoint was successful thyroid remnant ablation as assessed by the 8 (±1) month follow-up scan. Successful ablation was prospectively defined as a negative neck scan (no visible uptake or if visible less than 0.1% uptake in the thyroid bed).

With respect to this definition, successful thyroid remnant ablation was achieved in 100% of patients in the two groups. Using the much stricter criterion "no visible uptake" as required by the US Food and Drug Administration, successful ablation was achieved in 85.7% and 75.0% of patients in the THW group and Thyrogen group, respectively.

- ***Genzyme-sponsored studies: Ablation Follow-up study THYR01605 – study design***

THYR01605 was a follow-up study to THYR-008-00, with a median follow-up of 3.7 years. As its primary objective, THYR01605 sought to confirm the thyroid remnant ablation status in patients previously treated in THYR-008-00, using Thyrogen-stimulated dxWBS and static neck imaging. The same scanning protocol was used in THYR01605 as for the follow-up dxWBS in THYR-008-00.

In THYR01605 as well as in THYR-008-00, the ablation success criterion was no visible or <0.1% uptake in the thyroid bed, and scintigraphic images were classified according to the consensus of three independent expert readers blinded to the patients' THYR-008-00 treatment group.

Secondary objectives included confirmation of the status of thyroid remnant ablation using Thyrogen-stimulated serum Tg measurements and thyroid cancer recurrence in any of the patients since the end of the THYR-008-00 study.

Serum Tg <2 ng/ml on an immunometric assay with a 0.9 ng/ml functional sensitivity was the pre-specified definition of ablation success. Patients with potentially interfering TgAb levels were excluded from the Tg analysis.

Recurrence was assessed through a medical chart review by each patient's local investigator covering the period from the end of THYR-008-00 study ablation procedure until the end of THYR01605. The chart review was therefore mostly retrospective. The review comprised structured collection from the patient's medical record of all thyroid cancer-relevant test results and of information on any clinically significant medical events, thyroid cancer related or not.

The test results collected included those from all physical examinations, dxWBS, post-therapy WBS, serum Tg and TgAb measurements, neck ultrasonography, computed tomography, magnetic resonance imaging, positron emission tomography, and lymph node or neck mass needle aspiration cytologies or biopsies. Also collected were data on any radioiodine therapies, including the activities and TSH stimulation methods.

The investigators performing the chart review were not blinded to patients' THYR-008-00 treatment group. Based on the medical chart review as well as on all clinical data available at the time of the assessment, each patient's local investigator classified the patient as having definitive, possible or no evidence of DTC recurrence, or as being non-assessable for recurrence.

All but two of the 63 patients completing THYR-008-00 were eligible for THYR01605; two ineligible patients were excluded either because of a material protocol violation, namely, administration of only half the intended Thyrogen dose, in the pivotal study (n = 1), or because of diagnosis of distant metastasis based on scintigraphy performed 48-168 hr following ablation in THYR-008-00 (n = 1).

Of the 61 patients eligible for follow-up, 51 (83.6%) were enrolled, while the remaining 10 patients declined to enrol. Forty-eight of the 51 enrolled patients (78.7% of patients eligible for THYR01605) underwent static neck imaging and all 51 enrolled patients underwent medical chart review.

All patients evaluable for ablation success in both the original Thyrogen group (n= 25) and the original THW group (n = 18) had a 100% ablation success rate (95% CI calculation not applicable), based on meeting the primary endpoint of no visible or <0.1% visible uptake in the static neck scintigraphy.
The same 100% ablation success rate was present in both groups when patients who had received therapeutic radioiodine after THYR-008-00 (4 original Thyrogen and 5 original THW patients) were excluded from the analysis.

A total of 9 patients (in both treatment groups) received $^{131}$I therapy (approximately 100 mCi (3.7 GBq) or more) during the period between the end of the THYR-008-00 study and the initiation of this follow up study. These 9 patients commonly had neck nodal involvement known at the start of the THYR-008-00 study, although others had known tumour extension beyond the thyroid capsule at the time of thyroidectomy, or only slightly elevated serum Tg levels. Since the purpose of the follow-up scan was to assess the original remnant ablation effort during the THYR-008-00 study, patients who had received additional therapeutic radioiodine since the end of that study could confound the interpretation of the follow-up neck image done in the present study. When considering only the patients who did not receive radioiodine during the period between studies, it is still apparent that 100% of patients in both treatment subgroups (15 former Hypothyroid and 22 former Euthyroid patients) were successfully ablated.

If only the criterion of "no visible uptake" in the thyroid bed was applied, both groups had high ablation success rates, 84% (21/25) for the original Thyrogen group and 94% (17/18) for the original THW group. However, in a post hoc analysis, the 95% CI of the difference between the Thyrogen group and the THW group in "no visible uptake" rates was -28.3% to 7.4%. Thus the lower boundary of this confidence interval did not rule out the chance that the difference in these rates exceeded 20 percentage points, the maximum difference defining non inferiority.
After excluding the individuals receiving therapeutic radioiodine after THYR-008-00, 82% (18/22) original Thyrogen patients and 93% (14/15) original THW patients had no visible thyroid bed uptake (95% CI of difference in rates, -32.0% to 9.0%).

By the objective criterion of thyroid bed $^{131}$I percent uptake, all patients in both original study groups had negligible uptake, well beneath the 0.1% threshold of the primary endpoint. Median uptake was 0.006% (range, 0.003% to 0.066%) in the original Thyrogen patients (n = 25), and 0.005% (range, 0.003% to 0.039%) in the original THW patients (n = 18).

THYR01605 had as a secondary clinical efficacy-related endpoint a comparison of recurrence rates in patients who in THYR-008-00 had received Thyrogen assisted ablation versus those who had received THW-assisted ablation. The vast majority of patients in both groups were classified as recurrence-free in the nearly 4 years following the original ablation procedure:

- After a median 3.7 years (range 3.4 to 4.4 years) of follow-up, 93% (26/28) of the original Thyrogen group were classified as having no evidence of DTC recurrence, 4% (1/28) had possible evidence of recurrence and 4% (1/28) were considered "not assessable" for recurrence.
- After a median 3.8 years (range, 3.5 to 4.4 years) of follow-up, 96% (22/23) of the original THW group were classified as having no evidence of recurrence, and 4% (1/23) were considered "not assessable" for recurrence.

The one patient from the THYR-008-00 Thyrogen group who was classified as having possible evidence of recurrence was initially staged T2N1M0. Based on the scintigraphic primary endpoint and the serum Tg secondary endpoint, his thyroid remnant was considered successfully ablated at the THYR-008-00 follow-up. Between THYR-008-00 and THYR01605, he had several findings suggestive of neck disease on physical exam, neck ultrasonography, and THW- or Thyrogen-stimulated serum Tg assay. He received two 130 mCi radioiodine treatments and post-therapy WBS showed substantial thyroid bed uptake. In THYR01605, he had no visible thyroid bed uptake on static

neck scintigraphy or pathological uptake on dxWBS but was the only patient in the original Thyrogen group to have a Thyrogen-stimulated Tg >2 ng/ml (2.9 ng/ml).

Medical testing and $^{131}$I therapy following the THYR-008-00 study was for treatment of tumour already known or suspected to be present at the start of that study, rather than for recurrent tumour in patients who were believed to have been rendered disease-free after their initial diagnosis (or was for mildly and persistently elevated serum Tg levels). No patient had a definitive cancer recurrence, although 1 patient had possible cancer recurrence and 2 patients could not be assessed. Thus, 48/51 patients (94%) had no evidence of cancer recurrence.

- ***Investigator initiated Thyrogen-assisted ablation studies***

A literature search identified 12 investigator-initiated Thyrogen-assisted ablation studies that included and reported the results of primary or secondary clinical efficacy-related endpoints or both, were conducted in adults who, except for a handful of cases, had undergone near-total or total thyroidectomy for DTC and were published as or within peer-reviewed original reports. All were independent, except 1 partially Genzyme-supported (Taïeb, 2008, *Clin Endocrinol (Oxf)*)

The main study design characteristics of these studies are summarised in the following Table **1**.

The results of the trials which included at least 20 Thyrogen-treated patients evaluable for ablation success and that reported detailed ablation success criteria are summarised in Table 2.

**Table 1 - Key Study Design Characteristics of Thyrogen Ablation Studies Reporting Clinical Efficacy Related to Ablation Success Rates**

| **Study (Type)[a]** | **Evaluable patients, dxWBS (Tg)[other] criteria** | | **$^{131}$I ablation activity** | **Ablation success criteria** | | **Ablation success assessment timepoint, mos post-ablation** | **Comments** |
|---|---|---|---|---|---|---|---|
| | **Thyrogen** | **THW** | | **dxWBS** | **Tg** | | |
| ***Most Important Investigator-Initiated Studies (more than 8 Thyrogen-treated patients evaluable for efficacy)*** | | | | | | | |
| ***prospective, randomisation to Thyrogen vs. THW*** | | | | | | | |
| Chianelli 2008 | 21 (20) | 21 (20) | Thyrogen: 53.2 ± 4.9 mCi; THW: 54.6 ± 5.9 mCi | No visible uptake on follow-up THW dxWBS | THW Tg <1 ng/ml at follow-up if Tg >1 ng/ml at time of ablation | 6-12 mos | |
| Taïeb 2008 | 36 (36) | 35 (35) | 100 mCi | Thyroid bed uptake <0.1% on Thyrogen dxWBS | Thyrogen Tg <0.8 ng/ml | 9 ± 1 mos | |
| ***prospective, non-randomised or no randomisation to Thyrogen vs. THW*** | | | | | | | |
| Pacini 2002 | 70c (NA) | 50c (NA) | 30 mCi | No visible thyroid bed uptake on THW dxWBS | Not reported | 6-10 mos | Gave $^{131}$I at 48 hrs rather than 24 hrs post-Thyrogen course |
| Barbaro 2003; Barbaro 2006 d | 52 (52) | 41(41) | 30 mCi | Negative Thyrogen dxWBS | Thyrogen Tg <1 ng/ml | 12 mos | Used short stop of levothyroxine from the day before Thyrogen |

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|---|---|---|---|---|---|---|---|
| | | | | | | | course until the day after $^{131}I$ administration |
| Pilli 2007 | 72 (34) | NA | 50 mCi or 100 mCi (n = 36 each) | No visible thyroid bed uptake on Thyrogen dxWBS | Thyrogen Tg <1 ng/ml in absence of TgAb or detectable Tg at baseline | 6-8 mos | Randomised comparison of ablation success with Thyrogen + 50 mCi vs. Thyrogen + 100 mCi |
| **Retrospective** | | | | | | | |
| Robbins 2001; Robbins 2002d | 45 (NA) | 42 (NA) | Thyrogen: mean ± SD 110.4 ± 65.0 mCi; THW: 128.9 ± 74.0 mCi | No visible uptake on follow-up Thyrogen dxWBS (THW dxWBS in 5/42 THW patients) e | Not reported | Thyrogen: mean ± SD 10.8 ± 3.2 mos; THW mean ± SD 11.2 ± 2.5 mos | |
| Tuttle 2008 | 220b (NA) | 71b (NA) | Thyrogen: median 109 mCi (range 30-410 mCi) THW: median 103 mCi (range 29-368 mCi) | No visible uptake or <0.1% visible uptake on Thyrogen dxWBS | Not reported | 12-18 mos | Primary endpoint was short-medium-term DTC-related outcome |
| Rosário 2008 | NA (30) | NA (64) | 100 mCi | Not reported | Stimulated Tg (by the same method as was used with ablation) <1 ng/ml | 6-12 mos | Ablation success criterion also included no abnormalities on neck US; primary study endpoint was safety-related (radiation-induced damage) |
| ***Supportive Investigator-Initiated Studies*** | | | | | | | |
| **Prospective** | | | | | | | |
| Berg 2002 (Prospective) | [3] | [0] | 108 mCi | Not reported | Decreasing or stable, very low Tg concentrations | 6 mos | Pilot study; Ablation success criterion also included ≤0.1% uptake in post-ablation scan on Day 7 |
| Kovatcheva 2004 | [4] | [0] | Range: 89.2-118.9 mCi range | Not reported | Not reported | Not reported | Pilot study |

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|---|---|---|---|---|---|---|---|
| **Retrospective** | | | | | | | |
| Driedger 2006 | 2 (2) | 0 (0) | 62 mCi (n = 1) 68 mCi $^{131}$I (n = 1) | No thyroid bed uptake on follow-up Thyrogen dxWBS | Undetectable Thyrogen-stimulated Tg | 6 mos (n = 1)<br>36 mos (n = 1) | Case reports of patients with renal failure |
| Pitoia 2007 | [17] | [0] | Mean ± SD<br>92 ± 41 mCi (range 30-150 mCi) | Not reported | Not reported | Not reported | Re-ablated patients not successfully ablated under THW;<br>patients switched from levothyroxine to triiodothyronine 14-30 days before re-ablation |

$^{131}$I, $^{131}$-iodine; DTC, differentiated thyroid cancer; dxWBS, diagnostic whole-body scan; SD, standard deviation; Tg, serum thyroglobulin, THW, thyroid hormone withdrawal; US, ultrasonography

[a]Listed in descending order of number of evaluable Thyrogen patients

[b]Tuttle 2008 included 320 Thyrogen patients and 74 THW patients evaluable for the primary endpoint of DTC recurrence status; patients evaluable for ablation success included only those with a follow-up dxWBS at the authors' centre, Memorial Sloan-Kettering.

[c]Pacini 2002 also had a 42-patient treatment arm given ablation assisted by both Thyrogen and THW.

[d]Earlier publication reported results in an initial subgroup of a larger series of patients, later publication reported results for the entire sample of the same study.

[e] Definition of Robbins et al's "complete response" classification; these investigators also included a "partial response" classification that would correspond to unsuccessful ablation in THYR-008-00 and all other investigator-initiated studies that provided detailed descriptions of their dxWBS ablation success criteria

**Table 2 - Ablation success findings of THYR-008-00 and of selected published investigator-initiated Thyrogen-assisted ablation efficacy studies[a]**

| **Study** | **Arm: stimulation method + $^{131}$I activity** | **No. Evaluable[b] Pats.** | **Ablation success rates, % (proportion successfully ablated)** | | **Ablation success criteria and follow-up timepoint** | **Comments** |
|---|---|---|---|---|---|---|
| | | | **dxWBS** | **Tg** | | |
| ***Genzyme-sponsored study*** | | | | | | |
| THYR-008-00 (Pacini 2006) | Thyrogen + 100 ± 10 mCi | 32 | 100% (32/32)c | 95.8% (23/24)c | No visible uptake or <0.1% visible uptake on Thyrogen dxWBS; Thyrogen Tg <2 ng/ml in TgAb-negative patients; follow-up at 8 ± 1 mos | dxWBS ablation success rate, statistical tests of non-inferiority not applicable because rates the same in both groups; comparative Tg ablation success rate: P = 0.2341, $\chi 2$ test |
| | THW + 100 ± 10 mCi | 28 | 100% (28/28)c | 85.7% (18/21)c | | |
| ***Most Important Investigator-initiated studies (more than 8 Thyrogen-treated patients evaluable for efficacy)*** | | | | | | |
| **Prospective, randomisation to Thyrogen vs. THW** | | | | | | |
| Chianelli 2008 | Thyrogen + 53.2 ± 4.9 mCi | 21 | 90.5% (19/21) | 85.0% (17/20) | No visible uptake on THW dxWBS, THW Tg <1.0 | No significant intergroup differences in |

| | | | | | | |
|---|---|---|---|---|---|---|
| | THW + 54.6 ± 5.9 mCi | 21 | 95.2% (20/21) | 90.0% (18/20) | ng/ml in the absence of TgAb or detectable Tg at baseline; follow-up at 6-12 mos | ablation success rates, exact P values not reported |
| Taïeb 2008 | Thyrogen + 100 mCi | 36 | 94.4% (34/36) | 91.7% (33/36) | Thyrogen Tg <0.8 ng/ml, thyroid bed uptake <0.1% on Thyrogen dxWBS; follow-up at 9 ± 1 mos | |
| | THW +100 mCi | 35 | 100.0% (35/35) | 97.1% (34/35) | | |
| **Prospective, non-randomised or no randomisation to Thyrogen vs. THW** | | | | | | |
| Pacini 2002 | Thyrogen + 30 mCi | 70 | 54.0% (38/70) | Not reported | No visible thyroid bed uptake on THW dxWBS, Follow-up at 6-10 mos | Study gave $^{131}$I at 48 hrs rather than 24 hrs post-Thyrogen course; dxWBS ablation success rate, Thyrogen vs. THW, P <0.0001 Thyrogen vs. Thyrogen + THW, P <0.01 |
| | THW + 30 mCi | 50 | 84.0% (42/50) | Not reported | | |
| | Thyrogen + THW + 30 mCi | 42 | 78.5% (33/42) | Not reported | | |
| Barbaro 2003/ Barbaro 2006[e] | Thyrogen + 30 mCi | 52 | 76.9% (40/52) | 86.5% (45/52) | Negative Thyrogen dxWBS; Thyrogen Tg <1 ng/ml; follow-up at 1 yr | Thyrogen vs. THW dxWBS and Tg ablation success rates statistically equivalent; no P value reported; study used short stop of levothyroxine from day before Thyrogen course until day after $^{131}$I administration |
| | THW + 30 mCi | 41 | 75.6% (31/41) | 78.0% (32/41) | | |
| Pilli 2007 | Thyrogen + 50 mCi $^{131}$I | 36 | 88.9% (32/36) | 78.9% (15/19) | No visible thyroid bed uptake on Thyrogen dxWBS; Thyrogen Tg <1 ng/ml in absence of TgAb or detectable Tg at baseline; follow-up at 6-8 mos. | dxWBS ablation success rate, statistical tests of non-inferiority not applicable because rates the same in both groups; Tg ablation success rate: P = 0.46 |
| | Thyrogen + 100 mCi | 36 | 88.9% (32/36) | 66.6% (10/15) | | |
| **Retrospective** | | | | | | |
| Robbins 2001/ Robbins 2002e | Thyrogen + mean ± SD 110.4 ± 65.0 mCi $^{131}$I | 45 | 84.4% (38/45)f | Not reported | No visible uptake on follow-up Thyrogen dxWBS (THW dxWBS in 5/42 THW patients); follow-up at 10.8 ± 3.2 mos. in Thyrogen group, 11.2 ± 2.5 mos in THW group | No significant intergroup difference in dxWBS ablation success rate, exact P not reported |
| | THW + 128.9 ± 74.0 mCi $^{131}$I | 42 | 80.9% (34/42)f | Not reported | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Tuttle 2008 | Thyrogen + median 109 mCi (range 30-410 mCi) $^{131}$I | 220d | 94.5% (208/220) | Not reported | No visible uptake or <0.1% visible uptake on Thyrogen dxWBS; follow-up at 12-18 mos | Comparative dxWBS ablation success rates: P = 0.35 |
| | THW + median 103 mCi (range 29-368 mCi) $^{131}$I | 74 | 90.1% (64/71) | Not reported | | |
| Rosário 2008 | Thyrogen + 100 mCi | 30 | Not reported | 90.0% (27/30)f | Stimulated Tg (by the same method as was used with ablation) <1 ng/ml | No significant intergroup difference in ablation success rate, exact P not reported |
| | THW + 100 mCi | 64 | Not reported | 79.7% (51/64)f | | |

$^{131}$I, $^{131}$-iodine; dxWBS, diagnostic whole-body scan; Tg, serum thyroglobulin testing; THW, thyroid hormone withdrawal

[a]Listed in descending order of numbers of evaluable Thyrogen patients in a study. Pitoia 2007, Kovatcheva 2004, Berg 2002, and Driedger 2006, which totalled 25 evaluable Thyrogen ablation patients) are excluded from the present table because of small size (N < 20), because they did not report ablation success criteria in sufficient detail, or for both reasons.

[b]Evaluable based on dxWBS, Tg, or other criteria.

[c]The Genzyme-sponsored follow-up study THYR01605 confirmed the successful ablation of all evaluated patients from THYR-008-00 (n = 48 by dxWBS, Tg or both).

[d]Tuttle 2008 included 320 patients evaluable for the primary endpoint of DTC recurrence status; patients evaluable for ablation success included only those with a follow-up dxWBS at the authors' centre, Memorial Sloan-Kettering.

[e]Earlier publication reported results in an initial subgroup of a larger series of patients, later publication reported results for the entire sample of the same study.

[f] Patients with "complete response;" Robbins et al also included a "partial response" classification that would correspond to unsuccessful ablation in THYR-008-00 and all other investigator-initiated studies that provided detailed descriptions of their dxWBS ablation success criteria.

[g]In addition to stimulated Tg <1 ng/ml, the Rosário 2008 study included lack of abnormalities (and, presumably, thyroid remnants) on neck ultrasonography as part of its ablation success criterion.

Among those investigator-sponsored studies, the main supportive data comes from the ***Tuttle (2008) study*** which included results regarding DTC-related outcome using the following definitions:

1) No clinical evidence of disease (NCED): negative Thyrogen-assisted dxWBS at 6-18 months follow-up visit, and unstimulated Tg< 2 ng/ml, stimulated Tg< 10 ng/ml and no other clinical (including radiological) evidence of recurrence throughout follow-up.
2) Clinical recurrence: detection of metastases after a period of NCED.
3) Persistence disease: any of:
    a. unstimulated Tg≥ 2 ng/ml, stimulated Tg≥ 10 ng/ml at least 1 year post-ablation
    b. clinical (including radiological) persistence of known disease
    c. discovery of a metastasis within 6 months of ablation
    d. distant metastasis at diagnosis (5.6% of Thyrogen patients and 6.8% of THW patients in the Tuttle study had M1 disease at the time of thyroidectomy).
4) Thyroid bed uptake only: persistent thyroid bed uptake on the 6-18 months dxWBS without other evidence of persistent disease as described in category #3 above.

Mean duration of follow-up was 45 months for THW and 27 months for Thyrogen. The following results were reported:

**Table 3 - DTC-related outcome analysis, Thyrogen-assisted ablation versus thyroid hormone withdrawal-assisted ablation, Tuttle 2008 Study (J Nucl Med) (N=394)**

| Outcome classification | Thyrogen group (n = 324), % (n) | Thyroid hormone withdrawal group (n = 74), % (n) |
|---|---|---|
| *Primary Outcome Analysis*[a,b] | | |
| Clinical recurrence | 3.8% (12) | 6.8% (5) |
| NCED | 76.3% (244) | 62.2% (46) |
| Persistent disease | 15.9% (51) | 24.3% (18) |
| Thyroid bed uptake only | 4.1% (13) | 6.8% (5) |
| *Exploratory Outcome Analysis*[a,c] | | |
| Clinical recurrence | 3.8% (12) | 6.8% (5) |
| NCED | 73.8% (236) | 55.4% (41) |
| Persistent disease | 19.4% (62) | 32.4% (24) |
| Thyroid bed uptake only | 3.1% (10) | 5.4% (4) |

NCED, no clinical evidence of disease: negative Thyrogen 12-18 month follow-up dxWBS, all unstimulated Tg levels <2 ng/ml and all Thyrogen-stimulated Tg levels <10 ng/ml, without other clinical evidence of recurrence, throughout follow-up.
[a]The primary and exploratory outcome analyses differed only in that the Tg criterion for NCED or "thyroid bed uptake only" was unstimulated Tg <2 ng/ml and [a]Thyrogen-stimulated Tg <10 ng/ml in the primary analysis and unstimulated Tg <1 ng/ml and Thyrogen-stimulated Tg <2 ng/ml in the exploratory analysis.
[b] The distribution of outcome categories was not significant at $P = 0.10$, 2-sided Pearson $\chi^2$ test.
[c] The distribution of outcome categories was significant at $P = 0.021$, 2-sided Pearson $\chi^2$ test.

Further to the concerns raised by the CHMP that the number of patients with tumour stage T3-T4, N0-N1, M0 included was low and that results for specific stages were not separately presented, the MAH submitted the results of a post-hoc analysis performed by Dr Tuttle.

The main objective of this post-hoc analysis was to determine if the treatment effect was preserved in the identified subgroups. The following analyses (comparing Thyrogen to THW) have been conducted:

1. Clinical outcome in patients with T3/T4 disease
2. Clinical outcome in patients with N1
3. Clinical outcome in T3 N0, T3 N1, T4 N0 and T4 N1

**Table 4: Tuttle Database: Patients numbers: whole population and T3-T4 subgroups**

| | Thyrogen/n | THW/n | Total/n | % of total |
|---|---|---|---|---|
| **Whole population** | **320** | **74** | **394** | **100** |
| T1-T2 | 147 | 44 | 191 | 48.5 |
| T3N0 | 50 | 14 | 64 | 16.2 |
| T3N1 | 97 | 11 | 108 | 27.4 |
| T4N0 | 7 | 1 | 8 | 2 |
| T4N1 | 19 | 4 | 23 | 5.84 |

The same analysis as that conducted on the entire population was conducted in this subgroup post-hoc analyses. No significant differences based on preparation method were noted. As expected, recurrence rates were a little higher in both arms than in the overall population, but not substantially so.

*Clinical outcome in patients with T3/T4 disease (Thyrogen vs. THW)*

**Table 5: Clinical Outcome Status after Initial Ablation Using Suppressed Thyroglobulin of Less than 2 ng/ml and Stimulated Thyroglobulin of Less than 10 ng/ml to define NCED (ALL patients)**

| **Treatment** | **N** | **No Clinical Recurrence*** | **Clinical Recurrence** | **Persistent Disease** | **TB uptake only**** | ***P*** |
|---|---|---|---|---|---|---|
| rhTSH | 320 | 244 (76.3%) | 12 (3.8%) | 51 (15.9%) | 13 (4.1%) | |
| Hypothyroid | 74 | 46 (62.2%) | 5 (6.8%) | 18 (24.3%) | 5 (6.8%) | 0.10 |
| Total | 394 | 290 (73.6%) | 17 (4.3%) | 69 (17.5%) | 18 (4.6%) | |

* No Clinical Evidence of Disease (NCED) **TB= Thyroid bed

**Table 6: Clinical Outcome Status after Initial Ablation Using Suppressed Thyroglobulin of Less than 2 ng/ml and Stimulated Thyroglobulin of Less than 10 ng/ml to define NCED (T3/T4 patients only)**

| **Treatment** | **N** | **No Clinical Recurrence*** | **Clinical Recurrence** | **Persistent Disease** | **TB uptake only**** |
|---|---|---|---|---|---|
| rhTSH | 173 | 116 (67.1%) | 10 (5.8%) | 40 (23.1%) | 7 (4.0%) |
| Hypothyroid | 30 | 16 (53.3%) | 3 (10.0%) | 11 (36.7%) | 0 (0%) |
| Total | 203 | 132 (65.0%) | 13 (6.4%) | 51 (25.1%) | 7 (3.4%) |

* No Clinical Evidence of Disease (NCED) **TB= Thyroid bed

**Table 7: Clinical Outcomes a median of 2.5 Years After Initial Ablation Using Suppressed Thyroglobulin of Less than 1 ng/ml and Stimulated Thyroglobulin of Less than 2 ng/ml to define NCED (ALL patients)**

| **Treatment** | **N** | **No Clinical Recurrence*** | **Clinical Recurrence** | **Persistent Disease** | **TB uptake only**** | ***P*** |
|---|---|---|---|---|---|---|
| rhTSH | 320 | 236 (73.8%) | 12 (3.8%) | 62 (19.4%) | 10 (3.1%) | |
| Hypothyroid | 74 | 41 (55.4%) | 5 (6.8%) | 24 (32.4%) | 4 (5.4%) | 0.021 |
| Total | 394 | 277 (70.3%) | 17 (4.3%) | 86 (21.8%) | 14 (3.6%) | |

* No Clinical Evidence of Disease (NCED) **TB= Thyroid bed

**Table 8: Clinical Outcomes a median of 2.5 Years After Initial Ablation Using Suppressed Thyroglobulin of Less than 1 ng/ml and Stimulated Thyroglobulin of Less than 2 ng/ml to define NCED (T3/T4 patients only)**

| Treatment | N | No Clinical Recurrence* | Clinical Recurrence | Persistent Disease | TB uptake only** |
|---|---|---|---|---|---|
| rhTSH | 173 | 112 (64.7%) | 10 (5.8%) | 46 (26.6%) | 5 (2.9%) |
| Hypothyroid | 30 | 14 (46.7%) | 3 (10.0%) | 12 (40.0%) | 1 (3.3%) |
| Total | 203 | 126 (62.1%) | 13 (6.4%) | 58 (28.6%) | 6 (3.0%) |

* No Clinical Evidence of Disease (NCED) **TB= Thyroid bed

No significant difference between the 2 groups was observed by any statistical method used.

In order to compare the demographics and other key characteristics of the T3/T4 patients in the rhTSH group with those in the hypothyroid group, patient characteristics were analysed by unpaired t-testing for the continuous variable as set out below. None of these differences were statistically significant (see Table 9).

**Table 9: Group statistics (T3/T4 patients)**

| | | N | Mean | Std. Deviation | Std Error Mean |
|---|---|---|---|---|---|
| Age at time of ablation (years) | rhTSH | 173 | 51.3 | 16.5 | 1.25 |
| | THW | 30 | 48.0 | 14.7 | 2.68 |
| RAI activity (mCi) | rhTSH | 173 | 142.8 | 52.2 | 3.97 |
| | THW | 30 | 131.1 | 67.1 | 12.24 |
| 6 months Tg (suppressed) rhTSH (ng/mL) | THW | 153 | 3.8 | 17.4 | 1.41 |
| | | 26 | 24.8 | 105.7 | 20.73 |
| 12-18 months Tg (suppressed) | rhTSH | 170 | 7.4 | 48.5 | 3.72 |
| (ng/mL) | THW | 30 | 3.7 | 9.5 | 1.74 |
| 12-18 months stimulated Tg | rhTSH | 129 | 25.7 | 119.6 | 10.53 |
| (ng/mL) | THW | 27 | 22.4 | 86.8 | 16.70 |
| Tg @ final follow-up | rhTSH | 170 | 1858.5 | 22951.3 | 1760.28 |
| (ng/mL) | THW | 30 | 53.0 | 255.7 | 46.69 |
| RAI uptake at 48 hrs on f/u | rhTSH | 130 | 0.05 | 0.31 | 1760.28 |
| diagnostics WBS (%) | THW | 29 | 0.04 | 0.13 | 46.69 |

Comparison of the groups (rhTSH vs. hypothyroidism) with regard to several important categorical variables and did not reveal any difference between the groups with regard to gender, multifocality of tumour, distant metastases at diagnosis, primary histologic subtype, or N1/N0 status.

*Clinical outcome in patients with N1 disease (Thyrogen vs. THW)*

A comparison of patients with (N1), and without evidence of nodal involvement (N0) was perfomed to determine if nodal status affected the outcome when compared to the overall population:

**Table 10: Number of patients with N1 (ALL patients)**

| | Frequency | % | Valid % |
|---|---|---|---|
| rhTSH | 163 | 84 | 84 |
| THW | 31 | 16 | 16 |
| Total | 194 | 100 | 100 |

The results are shown in Table 11. The numerical trend is toward better outcomes with rhTSH, so this is not a significant issue.

**Table 11: Clinical Outcomes a median of 2.5 Years After Initial Ablation Using Suppressed Thyroglobulin of Less than 2 ng/ml and Stimulated Thyroglobulin of Less than 10 ng/ml to define NCED (N1 patients)**

| Treatment | N | No Clinical Recurrence* | Clinical Recurrence | Persistent Disease | TB uptake only** |
|---|---|---|---|---|---|
| rhTSH | 163 | 116 (65.0%) | 9 (5.5%) | 44 (27.0%) | 4 (2.5%) |
| THW | 31 | 13 (41.9%) | 4 (12.9%) | 12 (38.7%) | 2 (6.5%) |
| Total | 194 | 119 (61.3%) | 13 (6.7%) | 56 (28.9%) | 6 (3.1%) |

* No Clinical Evidence of Disease (NCED) **TB= Thyroid bed

Table 12 shows the results of a similar analysis using only N1 patients, which was performed using the stricter criteria.

**Table 12: Clinical Outcomes a median of 2.5 Years After Initial Ablation Using Suppressed Thyroglobulin of Less than 12 ng/ml and Stimulated Thyroglobulin of Less than 2 ng/ml to define NCED (N1 patients)**

| Treatment | N | No Clinical Recurrence* | Clinical Recurrence | Persistent Disease | TB uptake only** |
|---|---|---|---|---|---|
| rhTSH | 163 | 104 (63.8%) | 9 (5.5%) | 49 (30.1%) | 1 (0.6%) |
| THW | 31 | 8 (25.8%) | 4 (12.9) | 17 (54.8) | 2 (6.5%) |
| Total | 194 | 112 (57.7%) | 13 (6.7%) | 66 (34.0%) | 3 (1.5%) |

* No Clinical Evidence of Disease (NCED) **TB= Thyroid bed

*Clinical outcome in patients with T3N0 and T3N1 (Thyrogen vs. THW) and T4N0 and T4N1*

Similar analyses of T3N0and T3N1 patients comparing outcome under THW and Thyrogen were conducted. As before, there was no significant difference in clinical outcomes between Thyrogen and THW.

In the post-hoc analyses conducted in T4N0 and T4N1 groups, the numbers are very small, especially in the T4N0 category. These results should therefore be looked at with caution. That said, there were no significant differences between the groups.

**Table 13: Primary clinical outcomes in T3-4 N0-1 taking unstimulated Tg of <2 ng/ml or stimulated Tg of < 10 ng/ml as evidence of NCED (no clinical recurrence)**

| Primary outcome analysis: Tg-on < 2 ng/ml, stimulated Tg <10 ng/ml | | | | | | |
|---|---|---|---|---|---|---|
| TNM status | Stimulation method | n | No clinical recurrence (n/%) | Clinical recurrence | Persistent disease | TB uptake only |
| T3N0 | Thyrogen | 50 | 43 (86.0%) | 1 (2.0%) | 3 (6.0%) | 3 (6.0%) |
| | THW | 14 | 10 (71.4%) | 0 (-) | 4(28.6%) | 0 (-) |
| T3N1 | Thyrogen | 97 | 63 (64.9%) | 8 (8.2%) | 23 (23.7%) | 3 (3.1%) |
| | THW | 11 | 6 (54.5%) | 2 (18.2%) | 3 (27.3%) | 0 (-) |
| T4N0 | Thyrogen | 7 | 4 (57.1%) | 0 (-) | 3 (42.9%) | 0 (-) |
| | THW | 1 | 0 (-) | 0 (-) | 1 (100%) | 0 (-) |
| T4N1 | Thyrogen | 19 | 6 (31.6%) | 1 (5.3%) | 11 (57.9%) | 1 (5.3%) |
| | THW | 4 | 0 (-) | 1 (25.0%) | 3 (75.0%) | 0 (-) |

**Table 14: Secondary clinical outcomes in T3-4 N0-1 taking unstimulated Tg of <1 ng/ml or stimulated Tg of < 2 ng/ml as evidence of NCED (no clinical recurrence)**

| Secondary outcome analysis: Tg-on <1 ng/ml, stimulated Tg <2 ng/ml | | | | | | |
|---|---|---|---|---|---|---|
| TNM status | Stimulation method | n | No clinical recurrence (n/%) | Clinical recurrence | Persistent disease | TB uptake only |
| T3N0 | Thyrogen | 50 | 41 (82.0%) | 1 (2.0%) | 5 (10.0%) | 3 (6.0%) |
| | THW | 14 | 11 (78.6%) | 0 (-) | 3 (21.4%) | 0 (-) |
| T3N1 | Thyrogen | 97 | 61 (62%) | 8 (8.2%) | 27 (27.8%) | 1 (1.0%) |
| | THW | 11 | 3 (27.3%) | 2 (18.2%) | 6 (54.5%) | 0 (-) |
| T4N0 | Thyrogen | 7 | 4 (57.1%) | 0 (-) | 2 (28.6%) | 1 (14.3%) |
| | THW | 1 | 0 (-) | 0 (-) | 1 | 0 (-) |
| T4N1 | Thyrogen | 19 | 6 (31.6%) | 1 (5.3%) | 12 (63.2%) | 0 (-) |
| | THW | 4 | 0 (-) | 1 (25.0%) | 2 (50.0%) | 1 (25.0%) |

- Discussion on clinical efficacy

In this variation application, administration of Thyrogen as an adjunct for thyroid remnant ablation were proposed to be amended by the MAH with respect to:

- patients with tumour stage T3-T4, N0-N1, M0 and
- as an adjunct to thyroid remnant ablation with radioiodine activities other than 100 mCi (3.7 GBq).

The ablation success criteria no visible or <0.1% thyroid bed uptake and a TG level <2ng/ml used in these studies were already discussed and accepted during the Type II variation EMEA/H/C/220/II/18. Study THYR-008-00 formed the basis of approval of the current wording of the therapeutic indication limiting Thyrogen administration as an adjunct for ablation of thyroid remnant tissue to low risk patients in whom an activity of 100 mCi (3.7 Bq) radioactive iodine is used. No information regarding patients with other tumour stages or other ablation activities is available from this study.

Non-randomised prospective studies and retrospective studies were submitted to support this application, as well as two randomised clinical studies [Chianelli (2008) and Taieb (2008)]. However, it should be kept in mind that only published papers and no detailed information, such as study

protocols, are available. In addition, it is unknown whether these studies were performed in accordance with GCP.

The CHMP considered that the number of patients with tumour stage T3-T4, N0-N1, M0 included in the investigator-initiated prospective studies was low and results for patients with these specific stages were not separately reported in these papers. The MAH was requested to provide any further information on these specific subgroups to support the intended broadening of the therapeutic indication (deletion of "low risk").

In its response provided in writing and in an oral explanation, the MAH discussed mainly the retrospective study by Tuttle et al (2008) which included the highest number of patients with tumour stage T3 or T4. Particularly, the MAH provided the results of several post-hoc subgroup analyses conducted by the lead author of the published paper. In the Tuttle retrospective review, of the 320 patients treated with rhTSH, 45.9% were staged T3. The patients in the T3-T4 and N1 subgroups did not differ with respect to age, gender, tumour multifocality, N status and mean ablative activity. With respect to the clinical outcome in terms of clinical recurrence and persistent disease, the results in patients with T3-T4 tumours tended to be slightly inferior, compared to the whole study population, which is an expected finding. It is acknowledged that in the analyses of T3-T4 patients and N1 patients, the clinical outcome in the Thyrogen group tended to be similar or slightly better, compared to the THW group.

With regard to DTC-related outcome, based on the small number of patients in study THYR01605, no safety signal regarding tumour recurrence in Thyrogen-treated patients was detected. Data regarding short-medium DTC-related outcome are available from the retrospective study by Tuttle (2008) which investigated endpoints such as no clinical evidence of disease, clinical recurrence and persistent disease in addition to thyroid bed uptake. No long-term data regarding DTC outcome are available. Taking into account the retrospective design of the study and the considerably shorter duration of follow-up in Thyrogen-treated patients compared to the THW group, no definite conclusions are possible. At the most, it can be stated that no safety signal regarding tumour recurrence in Thyrogen-treated patients was detected in this study.

The results of other investigator-sponsored studies are considered only supportive and are summarised below:

Chianelli 2008: This is the only prospective randomised trial comparing Thyrogen to THW in patients in whom a radioiodine ablation activity of 54 mCi, i.e. lower than the activity of 100 mCi stated in the current therapeutic indication of Thyrogen, was used. Similar ablation success rates were observed in both groups. However, only low risk patients defined as “TNM stage pT1 larger than 1 cm or less than 1 cm in the presence of multiple foci” were included in this trial. In addition, as also stated by the authors, the results of this small study need to be confirmed in a larger series of patients.

Taieb 2008: The primary endpoint of this study was quality of life. Ablation success was evaluated as a secondary endpoint. The radioiodine ablation activity administered in this study was in accordance with the current approved therapeutic indication (i.e. 100mCi). Few patients with tumour stage T3N0-N1, M0 were included (Thyrogen n=4, THW n=8) and the results for this subgroup are not reported separately. No patients with T4 tumours were included.

Pilli 2007: The ablation success rates observed in patients treated with Thyrogen in this study are similar to other studies. However, patient with tumour stage T4/N0-N1/M0 were excluded and the number of patients with tumour stage T3/N0-N1/M0 is not stated. Thus, no conclusions regarding these subgroups are possible.

Robbins 2002: This trial had already been discussed during Type II variation EMEA/H/C/220/II/18.
With respect to the current Type II variation, it is of interest that 3 and 13 of 45 patients in the Thyrogen group had tumour stage T3 and T4, respectively. However, results for this subgroup are not reported separately. Ablation activity was determined individually for each patient. The mean activity administered in the Thyrogen group was 110 MCi, i.e. higher than stated in the currently approved

Thyrogen SPC. From the limited information available, it seems that few patients had received activities lower than 100 mCi.

Rosario 2008: The primary objective of this retrospective study was to study the damage caused by radioiodine for thyroid remnant ablation when used in combination with Thyrogen compared to THW. Ablation success was reported based on stimulated thyroglobulin levels and neck ultrasonography findings. This not considered as acceptable for the evaluation of efficacy of Thyrogen for pretherapeutic stimulation for ablation of thyroid tissue remnants. In addition, the activity for ablation used in this study was 100 MCi and (only) 9 patients with tumour stage T3 or T4 were included in the Thyrogen group. Thus, no conclusions with regard to the broadened therapeutic indication applied for in this Type II variations are possible.

In the trials by Pitoia (2007), Berg (2002) and Driedger (2006), the number of patients with tumour stage T3 or T4 is not stated. In the trial by Kovatcheva (2004) 2 patients and 1 patient with tumour stage T4N0M0 and T4N1M0, respectively, were included. Due to the small number of patients included in these trials and the limited information available from the publications, no conclusions regarding the efficacy of Thyrogen as an adjunct to radioiodine ablation therapy in the broadened therapeutic indication applied for can be drawn.

The CHMP considered that the data provided, particularly the requested subgroup analysis from the Tuttle study in patients with tumour stages T3-T4, N0-N1, were sufficient to support the deletion of the term "low risk" in the indication of remnant ablation in patients with well-differentiated thyroid cancer who do not have evidence of distant metastases. A multicentre randomised trial of high dose versus low dose radioiodine, with or without recombinant human thyroid stimulating hormone, for remnant ablation following surgery for differentiated thyroid cancer [Hilo] is currently ongoing in the UK (sponsored by Cancer Research UK). This study includes T1-T3, Nx, N0, N1, M0 patients. The MAH should commit to provide and discuss the results of this study, with particular focus on the patients with T3 tumours, as soon as available.

With regard to the use of lower radioiodine activity (30 mCi) for thyroid remnant ablation proposed by the MAH, one of the two available studies was negative and the other one inconclusive, due to a different posology. The CHMP considered that further large randomised studies are required to address this matter. The CHMP noted that two large prospective randomised studies of Thyrogen vs. THW for remnant thyroid ablation in patients with well-differentiated thyroid cancer are currently ongoing in the UK (mentioned above) and in France (ESTIMABL Study sponsored by the Institut Gustave Roussy), respectively. In the meantime, the CHMP considered that there is insufficient data available to agree on the changes to the recommendation for lower radioiodine activity as initially proposed by the MAH.

## 2.3 Clinical safety

Since the approval of Thyrogen to assist ablation, Thyrogen safety data has been reviewed from three main sources: Study THYR01605, the publications on the 12 investigator-initiated Thyrogen-assisted ablation studies and post-marketing safety surveillance data covering approximately 294,654 kits of Thyrogen distributed worldwide and approximately 295,046 patients treated with Thyrogen worldwide from 01 December 2003 – 30 November 2007.

- ***Genzyme-sponsored trial THYR01605***

A detailed formal adverse event (AE) analysis was provided from Study THYR01605 based on a 51-patient follow-up study to THYR-008-00.
In the Genzyme-sponsored trial THYR01605, treatment-emergent AEs were reported in 8 of 48 patients (16.7%) receiving Thyrogen in THYR01605. Nausea and dizziness occurred in 2 patients each. Diarrhoea, vomiting, asthenia, muscle spasms, disturbance in attention, headache, syncope,

insomnia, testicular swelling, sinus congestion, blister and increased tendency to bruise occurred in one patient each.

- ***Investigator initiated Thyrogen-assisted ablation studies***

An overview on the safety results reported in the publications on investigator-initiated studies is given in the following table.

**Table 15: Overview of AE Findings in Patients Given Thyroid to Assist Thyroid remnant Ablation Under Euthyroid Conditions, Investigator-Initiated Studies of Thyrogen-Assisted Ablation**

| Study (Reference) | Patients receiving Thyrogen to assist ablation under euthyroid conditions, n | Treatment-emergent AEs | Treatment-emergent SAEs | Thyrogen-related AEs | Thyrogen-related SAEs | Comments |
|---|---|---|---|---|---|---|
| *Independent investigator-initiated studies* | | | | | | |
| Tuttle 2008 (Tuttle, 2008, *J Nucl Med*) | 320 | No safety data reported. | No safety data reported. | No safety data reported. | No safety data reported. | AE assessment methods/results not reported. |
| Pilli 2007 (Pilli, 2007, *J Clin Endocrinol Metab*) | 72 | No safety data reported. | No safety data reported. | No safety data reported. | No safety data reported. | AE assessment methods/results not reported. |
| Pacini 2002 (Pacini, 2002, *J Clin Endocrinol Metab*) | 70 | No safety data reported. | No safety data reported. | No safety data reported. | No safety data reported. | AE assessment methods/results not reported. |
| Barbaro 2006 (Barbaro, 2006, *Nucl Med Commun*) | 52 | See "Thyrogen-related AEs" column. | None reported. | No significant side effects after Thyrogen administration.<br>No hypothyroid symptoms in Thyrogen patients despite 4-day stop in thyroid hormone from day before first Thyrogen injection till day after radioiodine administration; free levothyroxine normal at these two times. | None reported. | |
| Robbins 2002 (Robbins, 2002, *J Nucl Med*) | 45 | None reported | None reported | None reported | None reported | AE assessment methods/results not reported. |
| Rosário 2008 (Rosário, 2008, *Clin Endocrinol (Oxf)*) | 30 | Please see Table 2.7.4-1 for details on radiotoxicity. | None reported. | 1 patient (3.3%) had transient headaches with rhTSH. | None reported. | Study had as its primary endpoint salivary gland, gonadal, haematological and oxidative radiotoxicity with Thyrogen-assisted ablation vs. THW-assisted ablation. Frequency/severity of radiotoxicity consistently lower with Thyrogen, in many cases statistically significantly so. Please see Table 2.7.4-1 for details. |
| Chianelli 2008 (Chianelli, 2008, *Eur J Endocrinol*) | 21 | Nausea was most common radioiodine side effect; incidence not reported. Transient reduction of sense of taste in "few patients." No "significant side effects," no neck pain observed. Authors do not specify to which treatment group(s) these results apply. | None reported. | "The injection of rhTSH was well tolerated;" no other safety data included. | None reported. | |
| Pitoia 2007 (Pitoia, 2006, *Medicina (B Aires)*) | 17 | None observed. | None observed. | None observed. | None observed. | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Kovatcheva 2004 (Kovatcheva, 2004, *Nucl Med Rev Cent East Eur*) | 4 | None observed. | None observed. | Dizziness after the first Thyrogen injection in 1/10 (10.0%) patients receiving Thyrogen-assisted therapeutic $^{131}I$, a group that included the 4 patients undergoing ablation. The authors did not specify if the dizziness affected one of the ablation patients. | None observed. | Patients monitored for AEs by experienced medical staff in radiotherapy ward. |
| Berg 2002 (Berg, 2002, *J Endocrinol Invest*) | 3 | None observed in any ablation patient. | None observed in any ablation patient. | None observed in any ablation patient. | None observed in any ablation patient. | Patients monitored by experienced physicians and nurses during the week post-ablation, during which week they were hospitalised in the radiotherapy ward. |
| Driedger 2006 (Driedger, 2006, *Clin Nucl Med*) | 3 | None reported. | None reported. | None reported. | None reported. | Analysis of 3 patients on dialysis for renal failure receiving Thyrogen-assisted ablation. |
| Taieb 2008 (Taieb, 2008, *Clin Endocrinol (Oxf)*) | 37 | None reported other than those summarised in Table 2.7.4-6. | None reported. | Please refer to Table 2.7.4-6. | None reported. | Prospective, randomised QOL study that also monitored vital signs and 9 hypothyroid signs/symptoms in peri-ablation period and months 3, 6 and 9 after ablation. |

AE, adverse event; SAE, serious adverse event; THW, thyroid hormone withdrawal

The results of the study by Rosario (2008) with respect to radiation-induced damage are displayed in more detail in the following table:

**Table 16: Evaluation of Radiotoxicity Under Thyrogen-Assisted Ablation Versus Under THW-Assisted Ablation in the Rosario 2008 Study**

| Variable | Evaluation time | Exclusion criteria | Thyrogen group | THW group | *P* value, Thyrogen vs. THW (*P* < 0.05 = statistically significant)[a] |
|---|---|---|---|---|---|
| *Salivary gland radiotoxicity* | | | | | |
| Symptomatic acute sialoadenitis, incidence[b] | up to 7 days post-ablation | History of salivary gland disorders; use of anti-cholinergic drugs; recurrent or persistent salivary gland enlargement or pain pre-ablation; hyperamylasaemia pre-ablation | 30.0% (9/30) | 58.3% (35/60) | 0.01 |
| Hyperamylasaemia[b] (amylase >104 U/L) | 48 hr post-ablation | | 36.6% (11/30) | 80.0% (48/60) | <0.001 |
| *Gonadal radiotoxicity (men: testes, women: ovaries)* | | | | | |
| Follicle-stimulating hormone elevation (>14 U/L) | 6 mos post-ablation | History of chemotherapy, oophorectomy, pelvic radiotherapy; variocele or infertility; elevated follicle-stimulating hormone before ablation | | | |
| Men | | | | | |
| Incidence | | | 44.4% (4/9) | 88.9% (16/18) | 0.03 |
| Mean relative increase from baseline, % | | | 105% | 236% | <0.001 |
| Women | | History of chemotherapy, orchiepididymitis, cryptorchidism; variocele or infertility; elevated follicle-stimulating hormone before ablation | | | |
| Incidence | | | 7.7% (1/13) | 20.0% (6/30) | 0.4 |
| Mean relative increase from baseline | | | 65% | 125% | <0.001 |
| *Haematological radiotoxicity* | | | | | |
| Thyrombocytopaenia (platelets <100,000/mm$^3$) or neutropaenia (neutrophils <1,500/mm$^3$), incidence | up to 60 days post-ablation (measurements on days 30, 45 and 60 post-ablation) | Known haematological disease; neutrophils <1,800/mm$^3$, platelets <150,000/mm$^3$, or haemoglobin <12 g/dl before ablation | 7.1% (2/28) | 21.4% (12/56) | 0.1 |
| Mean relative decrease from baseline to nadir | | | | | |
| Platelets | | | 25% | 52% | <0.01 |
| Neutrophils | | | 20% | 45% | <0.01 |
| *Oxidative radiotoxicity* | | | | | |
| Plasma 8-Epi-Prostaglandin Factor$_{2\alpha}$ Elevation (>22 pg/ml) | 4 days post-ablation | Diabetes; smoker status | | | |
| Incidence | | | 56.0% (14/25) | 100.0% (45/45) | <0.001 |
| Mean relative increase from baseline | | | 60% | 125% | <0.001 |

THW, thyroid hormone withdrawal

[a] The Fisher exact test or the $\chi 2$ test were used to statistically compare the treatment groups with respect to proportions, while the Student *t* test or the Mann-Whitney U test were used to statistically compare the treatment groups with respect to means. However, the specific test used for each particular variable was not reported.

[b] All patients with symptomatic sialoadenitis up to 7 days post-ablation had hyperamylasaemia at 48 hr post-ablation

- ***Discussion on clinical safety***

No safety concerns are raised based on Study THYR01605.

The study by Rosario 2008 aimed specifically at evaluating radiation-induced salivary gland, gonadal, haematological and oxidative damage. In patients prepared with Thyrogen for thyroid remnant ablation, blood and whole body irradiation is lower compared to patients prepared by THW, most likely due to an approximately 50% greater clearance of radioiodine in euthyroid patients compared to hypothyroid patients. Thus, radiotoxicity is expected to be lower in Thyrogen-treated patients compared to patients prepared by THW. This was confirmed in the retrospective study by Rosario.

In the study by Taieb (2008) hypothyroid symptoms were evaluated and as expected, were observed less frequently in Thyrogen-treated patients than in the THW group in this study.

Except from these two studies, very limited information on safety is available from the published trials. In particular, neither in the prospective randomized study comparing Thyrogen to THW by Chianelli (2008) nor in the largest - albeit retrospective - study by Tuttle (2008), safety data are reported.

Further to completion of THYR01605, a new Integrated Summary of Safety was prepared by the MAH. As a consequence, the MAH proposed several updates to the safety information in sections 4.4 and 4.8 of the SPC, which were acceptable to the CHMP.

As the change to the indication will lead to a change to the patient population, the CHMP considered that PSURs should be submitted yearly, until otherwise specified by the CHMP.

## 3. Risk Management Plan

The MAH submitted a Risk Management Plan (RMP) in this variation application. A summary of the agreed version 5 of the RMP is provided in the table below:

**Table 17: Summary of the EU Risk Management Plan**

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation Activities (routine) |
|---|---|---|
| Gastrointestinal Symptoms | Routine: Post-marketing surveillance | Section 4.8 (Undesirable effects) SmPC derived from the CCSI:<br>The frequency of nausea, vomiting and diarrhoea are tabulated |
| Constitutional Symptoms | Routine: Post-marketing surveillance | Section 4.8 (Undesirable effects) SmPC derived from the CCSI<br>The frequency of headache, fatigue, dizziness and influenza-like illness are tabulated |
| Injection Site Reactions | Routine: Post-marketing surveillance | Section 4.8 (Undesirable effects) SmPC<br>Discomfort, pain, pruritis, rash and uticaria at the site of intramuscular injection are tabulated. |
| Hypersensitivity | Routine: Post-marketing surveillance | Section 4.3 (Contraindications) SmPC derived from the CCSI:<br>Hypersensitivity to human thyroid stimulating hormone or to any of the excipients.<br>Section 4.8 (Undesirable Effects) SmPC derived from the CCSI:<br>Manifestations of hypersensitivity have been reported uncommonly in both clinical and post-marketing settings. |

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation Activities (routine) |
|---|---|---|
| | | These reactions consisted of urticaria, rash, pruritis, flushing and respiratory signs and symptoms. |
| Neoplasm Swelling | Routine: Post-marketing surveillance | Section 4.4 (Special Warnings and Precautions for Use) SmPC derived from the CCSI:<br>Due to elevation of TSH levels after Thyrogen administration patients with metastatic thyroid cancer particularly in confined spaces such as the brain, spinal cord and orbit or disease infiltrating the neck, may experience local oedema or focal haemorrhage at the site of these metastases resulting in increased tumour size. This may lead to acute symptoms, which depend on the anatomical location of the tissue e.g. hemiplegia, hemiparesis, loss of vision have occurred in patients with CNS metastases. Laryngeal oedema, respiratory distress requiring tracheotomy, and pain at the site of metastasis have also been reported after Thyrogen administration. It is recommended that pre-treatment with corticosteroids be considered for patients in whom local tumour expansion may compromise vital anatomic structures.<br><br>Section 4.8 (undesirable effects) SmPC, includes the following text, inline with text in Section 4.4:<br>Enlargement of residual thyroid tissue or metastases can occur following treatment with Thyrogen. This may lead to acute symptoms, which depend on the anatomical location of the tissue. For example, hemiplegia, hemiparesis or loss of vision have occurred in patients with CNS metastases. Laryngeal oedema, respiratory distress requiring tracheotomy, and pain at the site of metastasis have also been reported after Thyrogen administration. It is recommended that pretreatment with corticosteroids be considered for patients in whom local tumour expansion may compromise vital anatomic structures.<br><br>A separate cumulative analysis of cases reporting thyroid swelling will be provided in the next PSUR. |
| Altered Pharmacokinetics in Patients with Advanced or End-Stage Renal Disease | Routine: Post-marketing surveillance | Section 4.2 (Posology and Method of Administration) SmPC derived from the CCSI:<br>Information from post marketing surveillance, as well as published information, suggests that elimination of Thyrogen is significantly slower in dialysis-dependent end stage renal disease (ESRD) patients, resulting in prolonged elevation of TSH levels for several days after treatment. This may lead to increased risk of headache and nausea. There are no studies of alternative dose schedules of Thyrogen in patients with ESRD to guide dose reduction in this population.<br>In patients with significant renal impairment the activity of radioiodine should be carefully selected by the nuclear medicine physician. |
| Medication Errors | Routine: Post-marketing surveillance | Section 4.2 (Posology and Method of Administration) SmPC derived from the CCSI:<br>The recommended dose regimen is two doses of 0.9 mg thyrotropin alfa administered at a 24-hour interval by intramuscular injection only.<br>Therapy should be supervised by physicians with expertise in |

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation Activities (routine) |
|---|---|---|
| | | thyroid cancer.<br>A separate review of medication errors during the reporting period of the next PSUR will be provided in the next PSUR |
| Neoplasm Growth<br>(Theoretical) | Routine: Post-marketing surveillance | Section 4.4 (Special Warnings and Precautions for Use) SmPC derived from the CCSI:<br>There is a theoretical possibility that Thyrogen, like thyroid hormone withdrawal, may lead to stimulated tumour growth. In clinical trials with thyrotropin alfa, which produces a short-term increase in serum TSH levels, no case of tumour growth has been reported |
| Cardiac Events in Patients with Intact Thyroid<br>(Off-label Use in Goitre Patients) | Routine: Post-marketing surveillance<br><br>Additional pharmacovigilance activity: A questionnaire will be implemented for all spontaneous reported cases to capture cardiovascular medical history. | Section 4.4 (Special warnings and precautions for use) SmPC derived from the CCSI:<br>Careful evaluation of benefit-risk relationships should be assessed for Thyrogen administration in high risk elderly patients who have heart disease (e.g. valvular heart disease, cardiomyopathy, coronary artery disease, and prior or current tachyarrhythmias including atrial fibrillation) and have not undergone thyroidectomy.<br><br>Thyrogen is known to cause a transient but significant rise in serum thyroid hormone concentration when given to patients who have substantial thyroid tissue still in situ. Therefore, careful evaluation of individual risk-benefit is necessary for patients with significant residual thyroid tissue.<br><br>Section 4.8 (Undesirable Effects) SmPC derived from the CCSI:<br>Very rare cases of hyperthyroidism or atrial fibrillation have been observed when Thyrogen 0.9 mg has been administered in patients with presence of either partial or entire thyroid gland.<br><br>A separate cumulative analysis of cases reporting cardiovascular adverse reactions will be provided in the next PSUR.<br>The next PSUR will include an evaluation of all cases which are potentially associated with off-label use, tracked by searching by indication as well as alternate dosages of Thyrogen used (i.e., lower doses used for the goitre indication). |
| TSH Decreased | Routine: Post-marketing surveillance | Section 4.2 (Posology and Method of Administration) SmPC derived from the CCSI:<br>For radioiodine imaging or ablation, radioiodine administration should be given 24 hours following the final Thyrogen injection. Diagnostic scintigraphy should be performed 48 to 72 hours following radioiodine administration, whereas post-ablation scintigraphy may be delayed additional days to allow background activity to decline.<br>For diagnostic follow-up serum thyroglobulin (Tg) testing, the serum sample should be obtained 72 hours after the final injection of Thyrogen. |

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation Activities (routine) |
|---|---|---|
| Anti-TSH antibodies in patients previously exposed to Bovine TSH | Routine: Post-marketing surveillance | Section 4.3 (Contraindications) SmPC derived from the CCSI:<br>Hypersensitivity to bovine thyroid stimulating hormone<br>Section 4.8 (Undesirable Effects) SmPC derived from the CCSI:<br>In clinical trials involving 481 patients, no patients have developed antibodies to thyrotropin alfa either after single or repeated limited (27 patients) use of the product. The occurrence of antibodies which could interfere with endogenous TSH assays cannot be excluded. |
| Use of Thyrogen in Pregnant Women | Routine: Post-marketing surveillance | Section 4.3 (Contraindications) SmPC<br>Pregnancy<br>Section 4.6 (Pregnancy and Lactation) SmPC derived from the CCSI:<br>Animal reproduction studies have not been conducted with Thyrogen.<br>It is not known whether Thyrogen can cause foetal harm when administered to a pregnant woman or whether Thyrogen can affect reproductive capacity.<br>Thyrogen in combination with diagnostic radioiodine whole body scintigraphy is contra-indicated in pregnancy, because of the consequent exposure of the foetus to a high dose of radioactive material. Patients should not breast-feed. |
| Use of Thyrogen and dosing in paediatric patients | Routine: Post-marketing surveillance | Section 4.2 (Posology) SmPC derived from the CCSI:<br>Due to a lack of data on the use of Thyrogen in children, Thyrogen should be given to children only in exceptional circumstances |
| Use of Thyrogen in remnant ablation using radioiodine activity below 100mCi | Routine: Post-marketing surveillance | Section 4.1 (therapeutic indication) SmPC<br>Use of Thyrogen for remnant ablation is restricted to combination with 100 mCi radioiodine only.<br>Section 4.4 (Special warnings and precautions for use) SmPC<br>In the pivotal trial of Thyrogen for pre-therapeutic stimulation before radioiodine ($^{13}$1I) ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer, an activity of 100 mCi (3.7 GBq) radioactive iodine ($^{131}$I) was used. Experience of rhTSH in combination with other radioiodine activities, in particular as low as 1 GBq is very limited. The efficacy of rhTSH for thyroid remnant ablation in combination with low radioiodine activities has not been demonstrated. |

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation Activities (routine) |
|---|---|---|
| Use of Thyrogen for remnant ablation in patients originally diagnosed with T3 thyroid cancer | Routine: Post-marketing surveillance<br><br>Additional activity: Submission of results from investigator sponsored study in the UK ('HiLo'), in particular in relation to patients with T3 thyroid cancer (post approval commitment from variation 38). | |
| Use of Thyrogen for remnant ablation in patients originally diagnosed with T4 thyroid cancer | Routine: Post-marketing surveillance<br><br>Additional activity: Submission of a protocol to collect data about remnant ablation in patients originally diagnosed with T4 thyroid cancer (post approval commitment from variation 38). | |

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

## 4. Benefit/risk assessment and recommendations

The CHMP agreed with the MAH that the term "low risk" in the current wording of the ablation indication is not well defined and does not precisely reflect the patient population studied in the pivotal study which led to the approval of Thyrogen for thyroid remnant ablation in thyroid cancer patients.

In this application, the MAH provided data on the clinical outcome of the subgroup of patients with tumour stage T3-T4, N0-N1 from the retrospective study by Tuttle et al. It is acknowledged that the reported results in the Thyrogen group do not seem to be inferior to the THW group. Based on a post hoc analysis, the MAH has provided reassurance regarding use in the subgroup T3-4, N0-1. Considering the relative rarity of the condition and the information provided in this application as well as these new additional data from the Tuttle 2008 study post-hoc analysis, the CHMP considered that the data are adequate to support of the variation.

The following changes to the ablation of thyroid remnant indication were therefore agreed by the CHMP:

*"Thyrogen is indicated for pre-therapeutic stimulation in combination with 100 mCi (3.7 GBq) ~~in low risk (see section 5.1) post-thyroidectomy patients maintained on hormone suppression therapy (THST) for the ablation of thyroid remnant tissue (in combination) with 100 mCi (3.7 GBq) radioactive iodine (131I).~~ radioiodine for ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastatic thyroid cancer."*

However, in the light of the limitations of the data and analyses, the MAH should commit to provide the results of the investigator sponsored study HiLo conducted in the UK, particularly with regard to T3 patients results. The MAH should also commit to conduct a study in T4 patients. The protocol of this study should be submitted to the CHMP for agreement.

With regard to radioiodine activities other than 100 mCi, there is currently no consensus on the lowest effective activity required for thyroid remnant ablation. Doubts remain regarding the efficacy of radioiodine activities at the low end of the currently administered range. Two large randomised studies of Thyrogen vs. THW and high vs. low radioiodine activity for thyroid remnant ablation in patients with thyroid cancer are currently conducted in UK and France. These trials are expected to provide important information with regard to the efficacy (including long-term outcome regarding thyroid cancer) of Thyrogen as an adjunct to remnant ablation as well as with regard to the radioiodine activity required for remnant ablation.

Until further data is available to support changes to the radioiodine activities to be used, it is recommended that the data available with regard to rhTSH in combination with low radioiodine activities are adequately reflected in section 4.4 of the SPC.

No safety concerns were raised based on this study THYR01605. Further to completion of THYR01605, a new Integrated Summary of Safety was prepared by the MAH. As a consequence, the MAH proposed several updates to the safety information in sections 4.4 and 4.8 of the SPC, which were acceptable to the CHMP. As the change to the indication will lead to a change to the patient population, the CHMP considered that PSURs should be submitted yearly, until otherwise specified by the CHMP.

Changes to sections 4.1, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics were consequently agreed by the CHMP. Annex II was updated to include the agreed version of the RMP and the change to the PSUR cycle. Minor editorial changes were made to the Labelling. The Package Leaflet was updated in accordance with the SPC and to update the list of local representatives.