Die Naturheilkunde
Volume 90.
www.forum-medizin.de ISSN 1613-3943

Reprint of the August 2013 issue

Thyreogym®

Final report

A prospective randomised placebo-controlled double-blind clinical trial to evaluate the efficacy and safety of Thyreogym

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Investigational product **Manufacturer**	Thyreogym (REF 5000) Thyreogym GmbH Lennestadt www.thyreogym.de	**Sponsor**	Rayonex Biomedical GmbH Sauerland-Pyramiden 1, 57368 Lennestadt Telefon: 02721 6006-0, Fax: 02721 6006-66 E-Mail: info@rayonex.de www.rayonex.de
Testing centre	Praxis Dr. med. Axel Schussmann Zur Ohe 2, 21406 Melbeck Telefon: 04134 900313, Fax: 04134 900483	**Study protocol**	klinische Studie Melbeck 2012 Rev.: 001 vom 16.10.2012
Thyroid ultrasonography	Dr. med. Göran Lönngren Facharzt für Allgemeinmedizin und für Palliativmedizin Am Diemel 19, 21406 Melbeck Telefon: 04134 248, Fax: 04134 8813	**Author**	Dr. med. Axel Schussmann Facharzt für Allgemeinmedizin
Statistician	Dipl.-Math. Ulrike Schulz, medistat GmbH Schauenburgerstr. 116, 24118 Kiel Telefon: 0431 88 88 701, Fax: 0431 88 88 700 E-Mail: info@medi-stat.de	**Standards and guidelines taken into account**	EN ISO 14155-1 MEDDEV 2.12/2 re2

Summary

Thyreogym is a weight loss device which relies on magnetic stimulation of the thyroid gland. This Class 2a medical device is made by Thyreogym GmbH and manufactured in accordance with Council Directive 93/42/EEC on medical devices (including amendments thereto by 2007/47/EC). The essential requirements of Appendix I are met and all other applicable harmonised standards have been applied. A Post-Market Clinical Follow-Up Study conducted in accordance with MEDDEV 2.12/2 re2 will help obtain further clinical data to support the efficacy and safety of Thyreogym. This clinical trial was conducted in accordance with Section 23b of the Medical Devices Act, and the two-part, internationally binding Good Clinical Practice (GCP) standard ISO 14155 "Clinical investigation of medical devices for human subjects - Part 1: General requirements (ISO 14155-1:2003)" and "Part 2: Clinical investigation plans (ISO 14155-2:2003)". The latter specifies requirements for the design, methodology and quality assurance of clinical trials on medical devices for all phases of development, and is equivalent to the GCP of the International Conference on Harmonisation (ICH-GCP) and Directive 2001/20/EC.1 The primary efficacy endpoint was the difference in body weight achieved after an eight-week period of use. Further, differences in body fat, skeletal muscle mass, BMI and visceral fat area were to serve as secondary efficacy endpoints. To this end, a prospective placebo-controlled randomised double-blind comparison of 33 obese patients with an unremarkable thyroid gland was conducted over the period from October 2012 to January 2013. The use of Thyreogym over eight weeks without any concurrent changes in lifestyle and eating habits resulted in an average weight loss of 2.0 kg in overweight individuals, while the control group gained an average of 0.9 kg over the same period. The 2.9 kg difference between the two groups was significant ($p < 0.01$). Along with the weight loss observed in the active treatment group and weight gain under placebo, reductions or increases with significant differences between groups were also observed for secondary efficacy endpoints. Thus, the difference between the two groups was 1.5 kg ($p = 0.030$) for body fat mass, 0.9 kg ($p = 0.011$) for skeletal muscle mass, 1.0 kg/m² ($p < 0.001$) for BMI and 6.1 cm² ($p = 0.012$) for the visceral fat area. There were no unexpected events or adverse events attributable to the use of Thyreogym. The efficacy and safety of Thyreogym could therefore be confirmed.

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A prospective randomised placebo-controlled double-blind clinical trial to evaluate the efficacy and safety of Thyreogym

In industrialised nations, excess weight, i.e. abnormal, excessive accumulation of body fat has become one of the greatest threats to the long-term health of the population. Over 1.4 billion people worldwide are considered overweight, and one third of them obese. In Germany, the prevalence of obesity has been rising steadily for decades; currently, around 16% of men and 14% of women in this country are considered obese. In those affected, this not only results in sometimes severely impaired quality of life, but is also associated with increased morbidity and mortality. The possibilities of modern magnetic therapy provide an innovative approach to lasting weight loss. A recent clinical study analysed the mode of action of pulsed electromagnetic fields for stimulation of the thyroid gland for the purpose of weight loss. The study was conducted using the magnetic therapy device known as Thyreogym (by Thyreogym GmbH) and confirmed the hypothesis that a magnetic field emitted by means of the therapy device can increase thyroid activity in test subjects and thereby achieve a long-term reduction in body weight. The following pages include the study report, present the study results and discuss the resulting implications for the therapeutic use of pulsed electromagnetic fields to achieve weight loss.

1. Health risks of obesity

The World Health Organisation (WHO) defines obesity based on the body mass index (BMI) and distinguishes three levels of severity: a person is considered obese from a BMI of 30 kg/m². Second level obesity is defined as a BMI from 35 kg/m² m, and morbid obesity is evoked from 40 kg/m². However, a person with a BMI from 25 kg/m² would already be considered overweight. What is known as pre-obesity is particularly prevalent in industrialised countries; it affects around two thirds of all men and more than half of women in Germany.2 Obesity is considered responsible for a number of secondary diseases; so-called 'diseases of civilisation' especially are often closely linked to severe obesity. The risk of cardiovascular diseases such as coronary heart disease3 and chronic heart failure4 thus increases along with the BMI, as does the risk of diabetes mellitus, certain cancers, lipometabolic disorders or musculoskeletal system disorders.

Recent studies also suggest that the risk of atrophy of certain areas of the brain, which heightens the risk of onset of dementia and Alzheimer's, also increases in correlation with BMI.5,6 In addition to these physical effects, the psychological consequences of severe obesity should not be underestimated. Young people especially are more likely to suffer from behavioural problems, depression and social exclusion. Experience has shown that due to the infamous yo-yo effect, diets tend to be counterproductive for long-term weight loss. Accordingly, the goal of any such treatments should always be lasting, slow and stepwise weight loss. Therapeutic efforts are therefore mostly geared towards sustainable changes in eating and exercising habits, but can also, as this study shows, be achieved by stimulation of the thyroid gland via pulsating electromagnetic fields.

2. Materials and methods

2.1. Investigational product

Thyreogym (REF 5000) is manufactured and sold by Thyreogym GmbH, Sauerland Pyramids 1, 57368 Lennestadt (Germany). It is an active, energy-releasing medical device categorised as Class IIa device in accordance with Rule 9 of Appendix IX to Directive 93/42/EEC.

The Thyreogym is a weight loss device which relies on magnetic stimulation of the thyroid gland. It hangs around the neck like a collar in a manner such that the neckline is level with the larynx. This area contains a coil which generates a magnetic field at a constant frequency. Thyreogym should be used one to three times a day for 30 minutes periods.

In the placebo devices, the coil of the Thyreogym which generates the therapeutic magnetic field is replaced by an ohmic resistor of the same size as the resistive component of the coil. This not only ensures that the placebo and the active device are outwardly indistinguishable from one another, but also that they consume the same amount of energy and thus have the same battery life. Further, the products are identical in terms of size, weight, shape, packaging, markings, signals, use, handling, cleaning, etc.

Fig. 1: A weight loss device which relies on magnetic stimulation of the thyroid gland: Thyreogym

2.2. Summary of the clinical investigation plan

2.2.1. Aim
This aim of this clinical study conducted in accordance with § 23b of the Medical Devices Act was to evaluate the efficacy and safety of Thyreogym for weight loss in overweight subjects.

2.2.2. Study design
The test was to be carried out as a prospective placebo-controlled randomised double-blind study. Weight loss was established as the primary endpoint. The secondary endpoint was a greater reduction in body fat compared to the reduction in skeletal muscle mass.

2.2.3. Data Quality Assurance
All documents and data were compiled and stored so as to ensure their control and protect the anonymity of the study participants to the appropriate extent.

The data gathered in this study were collected in paper form. A Case Report Form (CRF) was filled in for each patient, documenting the demographic data of the person, and whether criteria for inclusion and exclusion were met. The findings of the two thyroid ultrasounds, printed reports of the body composition analyses performed at the three data collection times and SAE forms were all attached to the CRF as appendices.

At the end of the tests, all records were entered into an anonymised Excel file, submitted to the two-person integrity test and made available to the statistician for unblinding and statistical analysis.

Upon completion of the study and statistical analysis, the CRFs and all other files were submitted to the sponsor for safekeeping over a period of at least 10 years from the end of the study.

2.2.4. Study population
According to the protocol, the study was to include 42 overweight men and women aged 25 to 65 years, with a BMI of 25 kg/m². Exclusion criteria were defined as known thyroid disease, intake of thyroid hormones, existing cancer, pregnancy or lactation, wearing a pacemaker or the presence of metal parts in the body (e.g. implants, screws, nails, etc.).

Potential study participants were recruited by Karin Schussman and Dr. Axel Schussman (GP) in the facilities of the Bioenergetic Therapy Centre and made aware of the study directly, either by the employees or by information leaflets laid out in the practice rooms. Those expressing an interest were informed about the study aims, its foreseeable risks, potential benefits, alternative therapies and confidentiality. Provided they gave their consent after an adequate reflection period and met the inclusion and exclusion criteria, these volunteers were enrolled in the study and assigned consecutive patient numbers. A case report form (CRF) was created for each patient enrolled in the study, and the relevant information entered therein by the principal investigator.

2.2.5. Treatment groups
The sponsor provided 42 testing devices (21 active devices and 21 placebo) for the study which were distributed according to a randomisation list in the first round.

2.2.6. Study procedure
A standard thyroid ultrasound was performed by Dr. Göran Lönngren in the Melbeck GP practice prior to the start of the study. This aimed to determine the size and volume of the thyroid gland, assess the tissue for the presence of lumps and abnormalities, and detect possible changes in the thyroid gland over the study period. Subjects with a normal thyroid who met all other inclusion and exclusion criteria were included in the study. At the first visit, they were assigned a testing device based on their randomised patient number, handed a patient diary and explained how to use the product. The first measurements were also collected. The patients were then reconvened for further measurements at four and eight weeks (±3 days). A further standard thyroid ultrasound was performed at the end of the study in order to detect potential changes in the thyroid gland over the study period.

2.2.7. Study variables
Changes in body weight [kg] were to be measured over the course of the study as the primary efficacy endpoint. The secondary efficacy endpoints were to be the differences achieved over the study period in the following parameters of the InBody 720 Body composition analysis:

- Body fat mass (kg)
- Skeletal muscle mass (kg)
- BMI (kg/m²)
- Visceral fat area (cm²)

2.2.8. Statistical analysis
The statistical analysis of the data aimed to confirm the null hypothesis that "the difference in weight achieved in the placebo group after eight weeks should be greater or equal to that achieved in the group using the active device". Alternatively, it was hypothesised that "the weight difference achieved in the placebo group would be less than the difference in the active treatment group".

The calculation of the sample size in the run-up to the study already factored in a drop-out rate. The study was to include 42 subjects (21 in each group). In order to demonstrate the relevant effect, that is, a 2.5 kg difference in weight between the two groups, 17 subjects were needed per study arm, assuming that the deviation of the difference was also 2.5 kg; four additional subjects were therefore factored into each group. The sample size calculation was based on the conservative assumption that two-sided tests would be performed. However, if using a one-sided test (as envisaged for the evaluation performed in this study), only 14 subjects would be required per group. This would also allow to compensate for a loss of power in the event of a non-parametric analysis.

An ITT analysis was performed for the statistical evaluation. As there were several drop-outs, the full analysis set was alternatively used for evaluation as the best possible approximation to the ITT collective.

The endpoints studied were presented descriptively using means and standard deviations, minimum and maximum values, and quartiles. Furthermore, the active device and placebo groups were compared with one another based on the differences achieved after four and eight weeks, and these differences initially tested using the Shapiro Wilk test for normal distribution. In the event of normal data distribution, the subsequent group comparison would be performed using the parametric t-test for independent samples. In the event of significant deviations from normal distribution, a comparison of the two treatment groups would be carried out using the Mann-Whitney U test.

The tests were two-sided and based on a level of significance of 5%. In order to maintain the required level of significance, an alpha adjustment was performed for multiple testing using the Holm–Bonferroni method. The IBM SPSS Statistics 21 (SPSS Inc., an IBM Company, Chicago, IL) software package was used to perform the statistical calculations.

3. Results

3.1. Study period

The study ran from 01 October 2012 to 31 January 2013. The thyroid ultrasounds were performed first. The eight-week treatments ran from mid-October to the end of December 2012, with three data collection points. Follow-up examinations of the thyroid gland were carried out until the end of January 2013.

3.2. Availability of patients and products

The study sponsor provided 42 testing devices (21 active devices and 21 placebo) which were numbered according to a randomised sequence and handed out to the patients enrolled in the study by the investigator.

A total of 38 patients (29 women and nine men) were included in the study, eight of whom did not initially meet the inclusion and exclusion criteria. Two patients were younger than 25 years, and two others older than 65 years. Given that Thyreogym should basically be used by adults and that these four patients were all deemed active and healthy by the investigator, they were included in the study regardless. Four other patients had a BMI which was slightly too low (24.0 to 24.9 kg/m²). The investigator chose to enrol them in the study regardless as they had recently experienced significant weight gain, especially in the months preceding the start of the study, and were expected to reach a BMI of 25.0 within a few weeks.

Five of the 38 patients enrolled stopped using the experimental device within the first four weeks, so that only 33 full sets of data were available for evaluation

3.3. Patient demographics

The demographic data of the patient sample enrolled in the study and evaluated are shown in Table 1. The FAS group consisted of 33 patients (24 women and nine men) with a mean age of nearly 47 years, an average height of 170.8 cm and an average weight of 90.28 kg. Fifteen patients were assigned to the treatment group while the other 18 were given a placebo device.

3.4. Adverse events and adverse effects of the product

In no patients were any adverse events or adverse effects of the product observed during the study. Neither were significant changes in the thyroid observed in the follow-up ultrasound examinations performed after the end of the study in any of the 33 patients (see sonography report of 30/01/2013 by Dr. Lönngren).

		ITT (intent-to-treat)			FAS (full-analysis-set)		
		gesamt	Placebo	Verum	gesamt	Placebo	Verum
Number	All	38	19	19	33	18	15
	female	29	14	15	24	13	11
	male	9	5	4	9	5	4
Age (years)	Ø	46,3	48,3	44,4	46,9	48,8	44,6
	Minimum	23	29	23	23	29	23
	Maximum	69	69	64	69	69	64
Size (cm)	Ø	170,6	170,5	170,7	170,8	170,2	171,5
	Minimum	156	156	159	156	156	163
	Maximum	190	186	190	190	186	190
Body weight (kg)	Ø	90,38	89,09	91,67	90,28	89,52	91,19
	Minimum	60,5	60,5	73,6	60,5	60,5	73,6
	Maximum	143,2	143,2	141,6	143,2	143,2	141,6

Table 1: Demographic data of patients (intent-to-treat and full-analysis-set samples)

3.5. Data analysis

3.5.1. Primary efficacy endpoint: Body weight

On average, patients treated with the Thyreogym lost 0.8 kg weight in the first four weeks of treatment, and a further 1.2 kg in the next four, while patients in the placebo group gained an average of 0.9 kg. The most significant weight loss in the active treatment group was 6.1 kg and the greatest weight gain was 1.0 kg. With the placebo, however, the weight reductions achieved ranged between -1.3 kg and +4.2 kg (Table 2; Figures 2 and 3). The differences between treatment groups with regard to weight differences achieved were significant both after four weeks (p = 0.009) and eight weeks (p <0.001) (Table 3). Half of the patients in the treatment group lost at least 2.3 kg, and a quarter of them even a minimum of 3.6 kg, while the median in the placebo group was +0.8 kg (Table 2).

Efficacy variable: Body weight

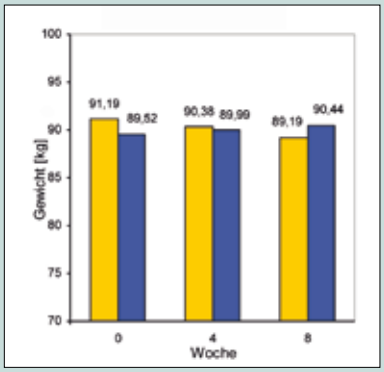
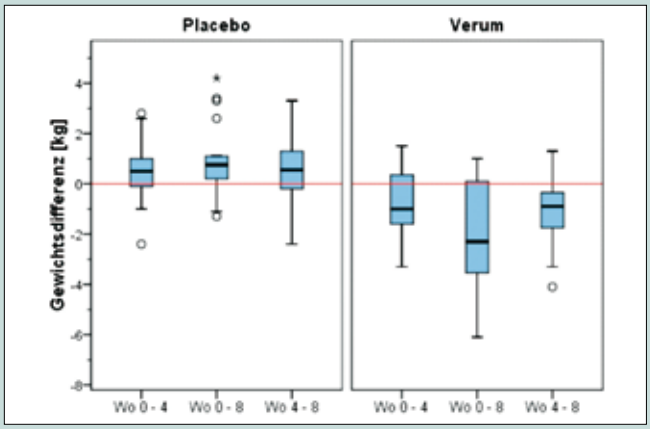


Figure 2: Average weight in the active treatment group (yellow) vs. the placebo group (blue) at baseline and after four and eight weeks of treatment.

Figure 3:
Box plot of the differences in weight between the different visits.



								Percentile		
	Group	Time	N	Mean	St. dev.	Min.	Max.	25.	50. (Median)	75.
Body weight	Placebo	Start	18	89,5	20,5	60,5	143,2	75,9	86,7	95,9
		Week 4	18	90,0	20,2	61,2	143,4	76,9	87,6	96,4
		Week 8	18	90,4	20,1	59,4	143,4	75,3	88,0	96,4
	Active device	Start	15	91,2	17,8	73,6	141,6	78,2	87,0	97,3
		Week 4	15	90,4	17,1	72,6	138,6	78,5	85,5	95,6
		Week 8	15	89,2	17,4	69,6	138,5	78,4	84,6	94,0
Weight difference	Placebo	Week 0–4	18	0,5	1,2	-2,4	2,8	-0,1	0,5	1,1
		Week 0–8	18	0,9	1,6	-1,3	4,2	0,1	0,8	1,5
		Week 4–8	18	0,5	1,4	-2,4	3,3	-0,2	0,5	1,3
	Active device	Week 0–4	15	-0,8	1,4	-3,3	1,5	-1,7	-1,0	0,4
		Week 0–8	15	-2,0	2,3	-6,1	1,0	-3,6	-2,3	0,1
		Week 4–8	15	-1,2	1,4	-4,1	1,3	-1,9	-0,9	-0,1

Table 2: Descriptive representation of the primary efficacy weight variable and weight difference achieved over the course of the study using the mean, standard deviation (St. Dev.), extreme values (min/max) and quartiles.

		Levene's test of equal variances		T-test comparing 2 means						
Body fat mass difference	variances homogenous	F	Sign.	T	df	Sign. (2-sided)	Mean difference	Standard error of the difference	95% confidence interval Lower	95% confidence interval Upper
Week 0–4	yes	0,999	0,325	2,808	31	p=0,009	1,280	0,455	0,350	2,209
	no			2,770	27,936	p=0,010	1,280	0,462	0,333	2,226
Week 0–8	yes	4,189	0,049	4,397	31	p<0,001	2,928	0,666	1,570	4,287
	no			4,254	24,249	p<0,001	2,928	0,688	1,508	4,349
Week 4–8	yes	0,025	0,876	3,285	31	p=0,003	1,648	0,501	0,625	2,672
	no			3,284	29,892	p=0,003	1,648	0,502	0,623	2,674

Table 3: Statistical difference in weight

3.5.2. 3.5.2. Secondary efficacy endpoint: Body fat mass

The decrease in body fat mass observed in patients who were using Thyreogym was almost 0.8 kg in the first four weeks, with a further 0.7 kg lost in the next four. In the placebo group, however, the body fat mass initially increased by an average of 0.3 kg, and then decreased again by 0.2 kg so that the value at the end of the study was close to the starting value of 34.2 kg (Table 4; Figures 4 and 5). The differences between treatment groups in terms of differences achieved were significant both after four weeks (p = 0.026) and after eight weeks (p = 0.030); however, no significant difference between groups could be detected in terms of the change in body fat mass between the fourth and eighth week (p = 0.256) (Table 5).

Efficacy variable: Weight Body fat mass

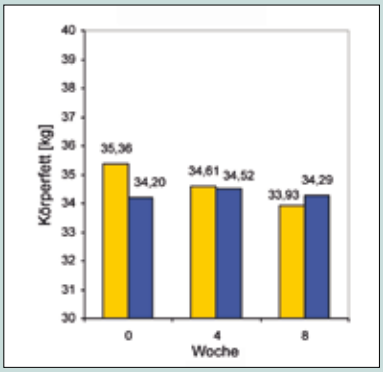
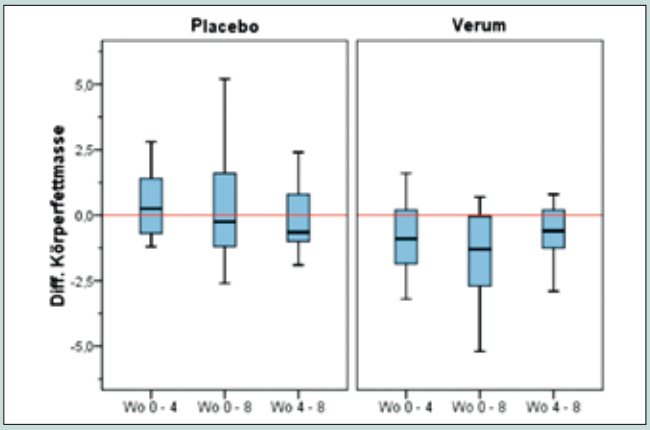


Figure 4: Average body fat mass in the active treatment group (yellow) vs. placebo (blue) at baseline and after four and eight weeks of treatment.

Figure 5: Box plot of the differences in body fat mass between the different visits.



	Group	Time	N	Mean	St. dev.	Min.	Max.	Percentile 25.	Percentile 50. (Median)	Percentile 75.
Body fat mass	Placebo	Start	18	34,2	13,5	17,5	72,7	24,5	30,3	41,9
		Week 4	18	34,5	13,8	18,6	73,1	23,9	31,5	41,6
		Week 8	18	34,3	13,7	19,3	71,9	23,5	32,3	41,9
	Active device	Start	15	35,4	11,2	18,7	54,6	27,7	32,4	43,4
		Week 4	15	34,6	10,4	20,1	51,5	28,0	33,7	42,1
		Week 8	15	33,9	10,5	17,4	50,7	27,0	33,1	42,2
Body fat mass difference	Placebo	Week 0–4	18	0,3	1,2	-1,2	2,8	-0,8	0,2	1,4
		Week 0–8	18	0,1	2,0	-2,6	5,2	-1,3	-0,3	1,7
		Week 4–8	18	-0,2	1,1	-1,9	2,4	-1,1	-0,7	0,8
	Active device	Week 0–4	15	-0,8	1,4	-3,2	1,6	-2,1	-0,9	0,3
		Week 0–8	15	-1,4	1,7	-5,2	0,7	-2,9	-1,3	0,1
		Week 4–8	15	-0,7	1,1	-2,9	0,8	-1,5	-0,6	0,3

Table 4: Descriptive representation of the secondary efficacy endpoint, i.e. body fat mass and difference in body fat mass achieved over the course of the study using the mean, standard deviation (St. Dev.), extreme values (min/max) and quartiles.

		Levene's test of equal variances		T-test comparing 2 means						
									95% confidence interval	
Body fat mass difference	variances homogenous	F	Sign.	T	df	Sign. (2-sided)	Mean difference	Standard error of the difference	Lower	Upper
Week 0–4	yes	0,428	0,518	2,334	31	p=0,026	1,076	0,461	0,136	2,015
	no			2,297	27,482	p=0,029	1,076	0,468	0,115	2,036
Week 0–8	yes	0,230	0,635	2,271	31	p=0,030	1,522	0,670	0,155	2,889
	no			2,305	30,969	p=0,028	1,522	0,661	0,175	2,869
Week 4–8	yes	0,209	0,651	1,158	31	p=0,256	0,447	0,386	-0,340	1,233
	no			1,162	30,272	p=0,254	0,447	0,384	-0,338	1,231

Table 5: Body fat mass stats

3.5.3. Secondary efficacy endpoint: Skeletal muscle mass

At baseline, the mean skeletal muscle mass of the patients in the active treatment group was 31 kg, vs. 30.7 kg in the placebo group. At the second visit, the value had dropped by 0.1 kg in the treatment group and increased by the same amount in the placebo group, so that the values in both groups were approximately the same (30.9 vs. 30.8 kg). This trend persisted in the second half of the study. Overall, under active treatment, the mean skeletal muscle mass decreased by 0.4 kg to 30.6 kg, while with the placebo, it increased by 0.5 kg to 31.2 kg (Table 6; Figures 6 and 7). The differences between treatment groups in terms of these efficacy endpoints were not significant after the first four weeks (p = 0.501); in contrast, the two groups differed significantly in terms of the difference achieved after eight weeks (p = 0.011). Even after adjustment for multiple testing, at P adj = 0.022, this difference could still be interpreted as significant. A comparison of the two treatment groups in terms of the difference obtained between the fourth and eighth week showed a significant difference between the active device and placebo groups (p = 0.010); this difference was also significant after adjustment for multiple testing, with P adj = 0.030 (Table 7).

Efficacy variable: Weight Skeletal muscle mass

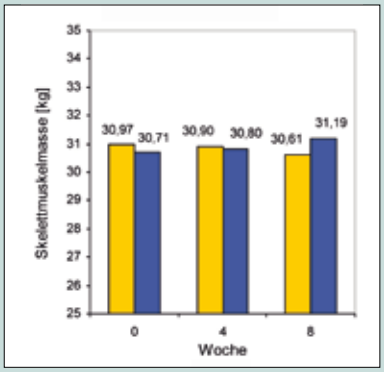
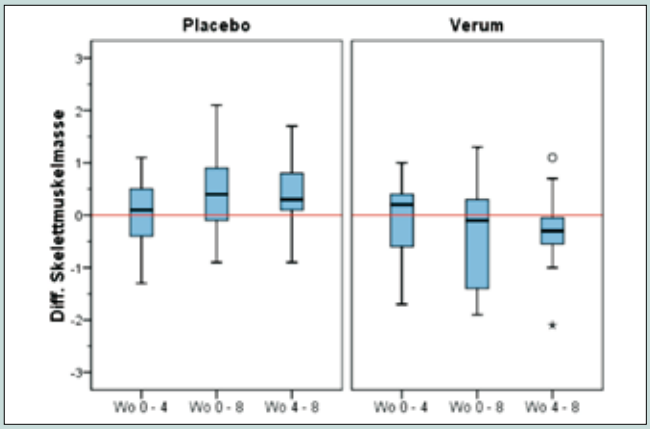


Figure 6: Average skeletal muscle mass in the active treatment group (yellow) vs. placebo (blue) at baseline and after four and eight weeks of treatment.

Figure 7: Box plots of the differences in skeletal muscle mass between the different visits.



								Percentile		
	Group	Time	N	Mean	St. dev.	Min.	Max.	25.	50. (Median)	75.
Skeletal muscle mass	Placebo	Start	18	30,7	6,9	21,2	50,7	26,3	29,1	33,0
		Week 4	18	30,8	6,7	22,2	49,9	26,8	28,5	33,3
		Week 8	18	31,2	6,8	21,8	50,4	26,7	28,9	34,1
	Active device	Start	15	31,0	6,4	24,8	49,7	26,3	29,7	34,6
		Week 4	15	30,9	6,5	25,0	49,9	26,6	30,6	34,4
		Week 8	15	30,6	7,0	22,9	51,0	26,0	30,4	34,4
skeletal muscle mass difference	Placebo	Week 0–4	18	0,1	0,7	-1,3	1,1	-0,4	0,1	0,5
		Week 0–8	18	0,5	0,8	-0,9	2,1	-0,1	0,4	0,9
		Week 4–8	18	0,4	0,7	-0,9	1,7	0,1	0,3	0,8
	Active device	Week 0–4	15	-0,1	0,8	-1,7	1,0	-0,6	0,2	0,5
		Week 0–8	15	-0,4	1,0	-1,9	1,3	-1,6	-0,1	0,5
		Week 4–8	15	-0,3	0,7	-2,1	1,1	-0,7	-0,3	0,0

Table 6: Descriptive representation of the secondary efficacy endpoint, i.e. skeletal muscle mass and difference in skeletal muscle mass achieved over the course of the study using the mean, standard deviation (St. Dev.), extreme values (min/max) and quartiles.

		Levene's test of equal variances		T-test comparing 2 means						
									95% confidence interval	
Body fat mass difference	variances homogenous	F	Sign.	T	df	Sign. (2-sided)	Mean difference	Standard error of the difference	Lower	Upper
Week 0–4	yes	0,775	0,385	0,681	31	p=0,501	0,168	0,246	-0,334	0,670
	no			0,672	27,928	p=0,507	0,168	0,250	-0,344	0,679
Week 0–8	yes	2,072	0,160	2,694	31	p=0,011	0,843	0,313	0,205	1,482
	no			2,627	25,822	p=0,014	0,843	0,321	0,183	1,503
Week 4–8	yes	0,009	0,926	2,742	31	p=0,010	0,676	0,246	0,173	1,178
	no			2,715	28,569	p=0,011	0,676	0,249	0,166	1,185

Table 7: Skeletal muscle mass stats

3.5.4. Secondary efficacy endpoint: Body Mass Index

At respectively 30.8 and 30.9 kg/m², the BMI was approximately the same in both treatment groups at baseline. After four weeks of treatment, this value had decreased by 0.2666 units in the Thyreogym group, while it had increased 0.344 units in the placebo group. This effect was even more pronounced after eight weeks: at study end, the BMI of the patients in the treatment group averaged 30.2 kg/m² and that of the placebo group, 31.1 kg/m²(Table 8; Figures 8 and 9). The differences between treatment groups with regard to BMI differences achieved were significant both after four weeks (p = 0.009) and eight weeks (p <0.001) (Table 5). In half of the patients in the active treatment group, an eight-week use of Thyreogym led to a reduction in BMI of at least 0.7 points, while the median in the placebo group showed a BMI increase of 0.3 points (Table 9).

Efficacy variable: Body Mass Index

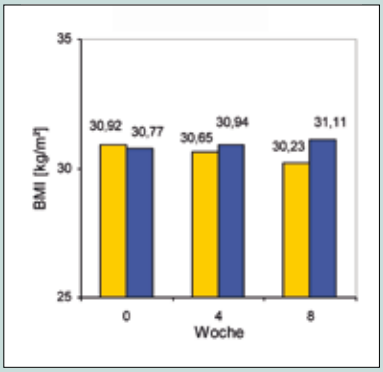
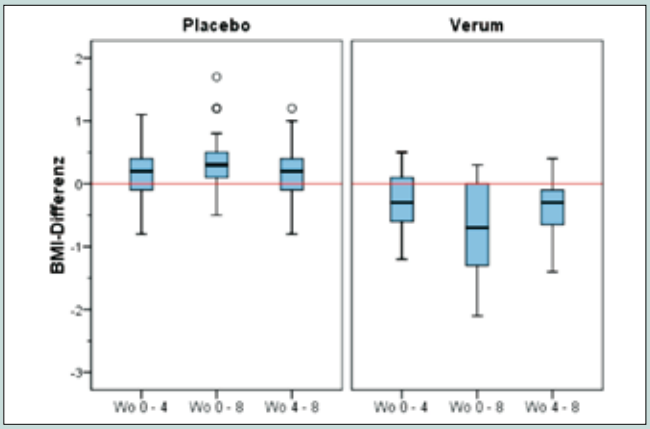


Figure 8: Average BMI in the active treatment group (yellow) vs. placebo (blue) at baseline and after four and eight weeks of treatment.

Figure 9: Box plots of BMI differences between the different visits.



								Percentile		
	Group	Time	N	Mean	St. dev.	Min.	Max.	25.	50. (Median)	75.
BMI	Placebo	Start	18	30,8	6,0	24,0	45,4	26,0	29,7	33,2
		Week 4	18	30,9	5,9	24,3	45,5	26,4	30,0	32,7
		Week 8	18	31,1	5,9	24,4	45,0	26,5	30,2	33,6
	Active device	Start	15	30,9	5,0	24,6	41,2	27,1	30,5	34,0
		Week 4	15	30,7	4,8	24,3	40,6	26,9	29,9	33,8
		Week 8	15	30,2	4,8	24,1	39,9	26,2	29,6	32,7
BMI-difference	Placebo	Week 0–4	18	0,2	0,4	-0,8	1,1	-0,1	0,2	0,4
		Week 0–8	18	0,3	0,6	-0,5	1,7	0,0	0,3	0,6
		Week 4–8	18	0,2	0,5	-0,8	1,2	-0,1	0,2	0,4
	Active device	Week 0–4	15	-0,3	0,5	-1,2	0,5	-0,6	-0,3	0,1
		Week 0–8	15	-0,7	0,8	-2,1	0,3	-1,3	-0,7	0,0
		Week 4–8	15	-0,4	0,5	-1,4	0,4	-0,7	-0,3	0,0

Table 8: Descriptive representation of the secondary efficacy endpoint BMI and difference in BMI achieved over the course of the study using the mean, standard deviation (St. Dev.), extreme values (min/max) and quartiles.

		Levene's test of equal variances		T-test comparing 2 means						
Body fat mass difference	variances homoge-nous	F	Sign.	T	df	Sign. (2-sided)	Mean difference	Standard error of the difference	95% confidence interval Lower	95% confidence interval Upper
Week 0–4	yes	0,855	0,362	2,796	31	p=0,009	0,439	0,157	0,119	0,759
	no			2,770	28,644	p=0,010	0,439	0,158	0,115	0,763
Week 0–8	yes	2,595	0,117	4,372	31	p<0,001	1,038	0,237	0,554	1,522
	no			4,258	25,582	p=0,000	1,038	0,244	0,536	1,539
Week 4–8	yes	0,014	0,908	3,367	31	p=0,002	0,599	0,178	0,236	0,962
	no			3,376	30,230	p=0,002	0,599	0,177	0,237	0,961

Table 9: Statistical difference in BMI

3.5.5. Secondary efficacy endpoint: visceral fat area

As regards the visceral fat area (VFA), there were marked differences between the two groups at baseline. The mean VFA was 141.7 cm² in the active treatment group and 134.2 cm² in the placebo group. After four weeks of treatment, the value decreased in both groups, by respectively 0.6 cm² (active treatment) and 0.4 cm² (placebo). In the second half of the study, the VFA in the active treatment group fell by a further 3.1 cm², while in the placebo group, it rose again by 2.9 cm². After four weeks, the difference in these differences was not significant (t-test for independent samples, p = 0.933). In contrast, a significant difference between groups was observed after eight weeks (p = 0.012). Even after adjustment for multiple testing, at P adj = 0.036, this difference could still be interpreted as significant. A comparison of the two treatment groups in terms of the difference obtained between the fourth and eighth week showed a significant difference between the active device and placebo groups (p = 0.035), although this difference was no longer significant after adjustment for multiple testing, with P adj = 0.070 (Table 11).

Efficacy variable: visceral fat area

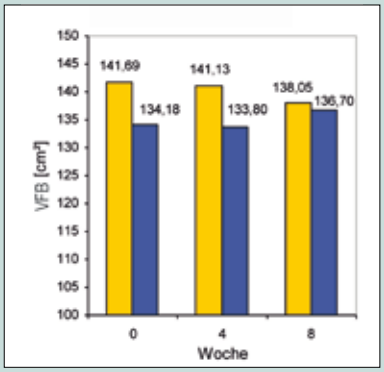


Figure 10: Average VFA in the active treatment group (yellow) vs. placebo (blue) at baseline, and after four and eight weeks of treatment.

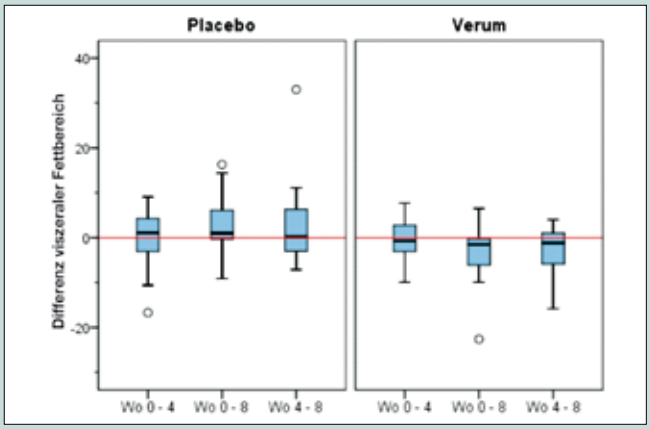


Figure 11: Box plots of differences in VFA between the different visits.

	Group	Time	N	Mean	St. dev.	Min.	Max.	Percentile 25.	Percentile 50. (Median)	Percentile 75.
VFB	Placebo	Start	18	134,2	38,5	85,8	214,4	104,6	126,8	163,0
		Week 4	18	133,8	36,6	86,7	216,1	103,4	128,4	159,3
		Week 8	18	136,7	40,9	82,0	230,7	103,1	130,9	165,0
	Active device	Start	15	141,7	34,9	82,2	215,5	120,9	135,5	171,4
		Week 4	15	141,1	33,9	84,9	205,6	124,7	139,8	171,5
		Week 8	15	138,0	36,3	72,5	209,6	110,3	142,0	167,8
VFB-difference	Placebo	Week 0–4	18	-0,4	6,5	-16,7	9,1	-3,8	1,1	4,3
		Week 0–8	18	2,5	6,3	-9,1	16,3	-0,8	0,9	6,2
		Week 4–8	18	2,9	9,1	-7,1	33,0	-3,0	0,1	6,8
	Active device	Week 0–4	15	-0,6	4,7	-9,9	7,7	-3,7	-0,7	2,8
		Week 0–8	15	-3,6	6,9	-22,6	6,5	-6,3	-1,5	-0,2
		Week 4–8	15	-3,1	5,8	-15,8	4,0	-6,6	-1,2	1,1

Table 10: Descriptive representation of the secondary efficacy endpoint "visceral fat area" (VFA) and difference in VFA achieved over the course of the study using the mean, standard deviation (St. Dev.), extreme values (min/max) and quartiles. (all data in cm²)

		Levene's test of equal variances		T-test comparing 2 means						
									95% confidence interval	
Body fat mass difference	variances homogenous	F	Sign.	T	df	Sign. (2-sided)	Mean difference	Standard error of the difference	Lower	Upper
Week 0–4	ja	1,338	0,256	0,085	31	p=0,933	0,170	2,000	-3,909	4,249
	nein			0,088	30,431	p=0,931	0,170	1,941	-3,792	4,132
Week 0–8	ja	0,005	0,942	2,680	31	p=0,012	6,157	2,297	1,472	10,842
	nein			2,657	28,770	p=0,013	6,157	2,317	1,417	10,897
Week 4–8	ja	0,649	0,427	2,204	31	p=0,035	5,987	2,717	0,446	11,527
	nein			2,292	29,231	p=0,029	5,987	2,612	0,647	11,327

Table 11: Visceral Fat Area stats

4. Discussion of results

The causes of overweight and the obesity that develops as a result are complex; the potential health consequences remain the same. Whether modern lifestyles, which are characterised by a lack of exercise and lots of high-calorie food are to blame for overweight, whether there is a familial predisposition, or whether excessive stress or the side effects of medications are what causes excess BMI, the risk for many diseases is increasing steadily and exponentially, especially as regards so-called diseases of civilisation. The prevalence of obesity worldwide has been increasing steadily for years, and we can consequently expect supply shortages and cost increases in health care systems. Due to its high tendency to recur, it also requires appropriate long-term and dynamic therapy concepts which should aim to ensure sustained weight control beyond the actual weight-loss phase. The stabilisation of one's body weight and a moderate reduction of 5-10% thereof should thus be favoured over striving for ideal or standard weight.

Moderate weight loss without the yo-yo effect

This is the kind of moderate weight reduction that was achieved in this study. Using Thyreogym, patients lost an average of two kilograms within eight weeks, without any concomitants change in lifestyle or eating habits. This moderate weight loss is generally considered very healthy by doctors and nutritionists, as it excludes the so-called yo-yo effect and allows longer-term success to be achieved. An observational study of 41 overweight patients carried out in spring 2012 8 had already showed that the use of Thyreogym allowed to achieve moderate weight loss. In the present case, an average weight loss of about three kilograms was achieved in four weeks. However, the values can not be compared directly, given that in the observational study, as well as using the Thyreogym, study participants also took the dietary supplement Thyreovital twice daily and had been asked to adhere to a healthy diet according to the nutrition guide "The right diet for your thyroid". On the other hand, the weight reduction of "just" 2 kg achieved in this study in the treatment group should be compared with the simultaneous weight gain of 0.9 kg observed in the placebo group. This could be attributed to the fact that the study was conducted between October 2012 and December 2012, probably the most difficult time of the year to lose weight.

Results for secondary efficacy endpoints

Along with the weight loss observed in the active treatment group and its increase under placebo, significant differences were also observed between groups in relation to secondary efficacy endpoints such as body fat, skeletal muscle mass, BMI and visceral fat area. The difference between the differences achieved in terms of body fat and skeletal muscle mass is particularly worthy of mention: during the eight-week use of Thyreogym, the skeletal muscle mass of the patients only decreased by about 0.4 kg, while their body fat mass dropped by almost three times that value (1.4 kg). However, metabolic and cardiovascular health risk are determined not only by the degree of obesity, which is defined based on BMI, but also by body fat distribution. In physiognomic terms, a distinction is made between so-called "apple-shaped" people, who carry most of their weight around the stomach, and "pear-shaped" types who are heavier around the hips and thighs. There is a close correlation between intra-abdominal (or visceral) fat, and cardiovascular risk factors and complications; it is thus considered a key indicator of metabolic syndrome. Among other things, the InBody body composition analysis conducted in this study also determined the visceral fat area. A value of more than 100 cm² was considered high. As shown in Figure 12, the VFA of almost all study participants was already either elevated or very high at baseline. Eight-week use of Thyreogym resulted in a reduction in VFA in 75% of the patients in this group. On average, a reduction of 3.6 cm² was achieved, while an increase of 2.1 cm² was observed in the placebo group over the same period.

Further results regarding treatment with PEMF therapy

After more than four decades of intensive clinical research, the use of pulsed electric-magnetic fields (PEMF) therapy has been demonstrated as beneficial in the treatment of various diseases, with particularly good results achieved in the treatment of arthritis, osteoarthritis, sciatica and neuropathies. However, their exact mode of action on physiological processes remains unclear.9 Numerous findings support the theory of increased cell proliferation through enhanced gene expression and the formation of growth factors. 9,10,11 This effect has also been demonstrated in vitro, in association with the use of Thyreogym, in various cell cultures. Treatment with Thyreogym was shown to shift the entire cell cycle of human keratinocytes (HaCat) back towards active cell division.

Des Further, this series of studies showed, impressively, that PEMF generated traceable and measurable metabolic activation of human fibroblasts (AG01522) and human keratinocytes (HaCat)12. Based on a general overview of the literature on PEMF therapy, it can be seen that a modest stimulation in metabolism is achieved in the most diverse cell types. This also explains the efficacy of Thyreogym in overweight individuals. In addition to overeating, lack of exercise and excessively low energy expenditure, metabolic disorders most of all are worth highlighting as one of the main causes of obesity. These include thyroid dysfunction, one of the most common of all hormone disorders.

Animal studies have shown that the thyroid is sensitive to low frequency electromagnetic fields.13 Results from human studies have confirmed that longer-term exposure to magnetic fields has no effect on the endocrine function of the thyroid gland 14 and does not increase the risk of thyroid disease.15

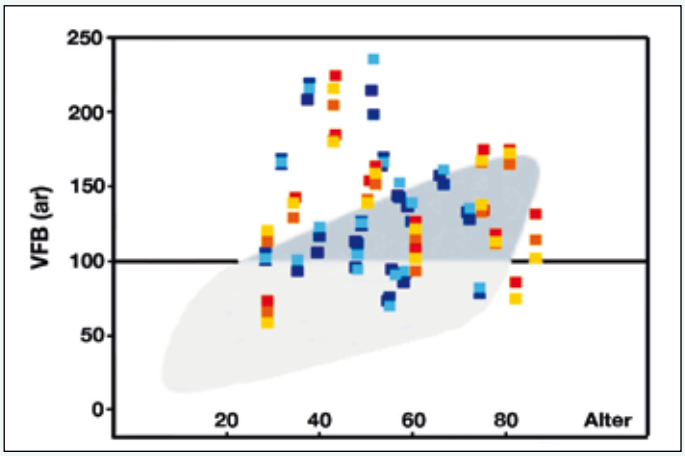


Figure 12: Visceral fat area values The grey cloud represents the average visceral fat area of the general population The values measured in the patients are shown as coloured dots (dark orange: Active device/1. Visit; orange: Active device/2. Visit; yellow: Active device/3. Visit; dark blue: Placebo/1. Visit, medium blue: Placebo/2. Visit, light blue: Placebo/3. visit). Values> 100 cm² are considered increased, and those above the grey cloud as greatly increased.

In a pilot study conducted in 200916, 13 overweight patients with moderately pronounced hypothyroidism (10 active treatment, 3 placebo) used Thyreogym once daily over a four-week period. In this longitudinal study, the patients were blinded to the experimental device. The study variables used were the serum concentrations of the thyroid hormones TSH, fT3 and fT4 at baseline and study end. Statistical analysis using the t-test revealed significant changes in TSH, fT3 and fT4 concentrations typically associated with thyroid gland activation. No statements were made regarding the body weight of the patients.

The data collected as part of this clinical study suggest that the use of Thyreogym achieved gentle, moderate activation of the thyroid gland. The side effects typically observed with thyroid-stimulating medications were not observed.

5. Concluding assessment

In summary, this Post Market Clinical Follow-Up Study conducted in accordance with MED-DEV 2.12/2 re2 as a prospective placebo-controlled randomised double-blind comparative study demonstrated the efficacy of Thyreogym. The results speak for the benefit of using pulsed electromagnetic fields (PEMF) as a complementary therapy to stimulate the thyroid gland in order to lose weight. The study also allowed to confirm the safety of the medical device. There were no unexpected events or adverse events attributable to the use of Thyreogym.

Fußnoten

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