2. SYNOPSIS OF THE STUDY'S FINAL REPORT

Name of the Promoter	*Commercial product name*	*Name of the active ingredient*
Manetti & Roberts	Somatoline ®	Levothyroxine (100 mg) and Aescin (300 mg) per 100 g of product

Title of the study

PILOT CLINICAL STUDY ON THE SYSTEMIC BIOAVAILABILITY OF L-THYROXINE IN HEALTHY VOLUNTARY WOMEN AFTER FOUR WEEKS OF TOPICAL TREATMENT WITH A NEW FORMULATION OF L-THYROXINE.

Principal investigators and research centers

The study took place in Italy and involved a single center: Prof. Maurizio Bevilacqua, Endocrinology Unit, Luigi Sacco Hospital, via Giovanni Battista Grassi 74, 20 157 Milan (Italy).

Publication (reference)	*Phase of the study*
Not published (2010)	Phase 4
Date of enrollment of the first subject	***Date of completion of the last subject***
09 May 2011 (first visit of the first volunteer).	07 July 2011 (last visit of the last volunteer.)

Targets

Primary goal

Evaluation of the systemic bioavailability of free l-thyroxine (FT_4) in healthy women after application of a new formulation of Somatoline ® according to the dosage prescribed by the AIC.

Secondary objectives

Evaluation of the systemic bioavailability of T_3, rT_3 and TSH in the same experimental conditions indicated for the primary objective.

Evaluation of the local and systemic safety and tolerability of the product.

Study design

A pilot study, single-center, prospective longitudinal, uncontrolled, lasting 42 days in a cohort of 20 healthy adult women. After identifying an adequate pool of potential subjects, the enrollment period was expected to end in approximately 10 weeks, equal to a recruitment rate of approximately two subjects per week.

The treatment lasted a total of 28 days, of which the first with an attack dose and the following maintenance. This was followed by a follow-up period of 14 days, for a total study duration of 42 days for each subject. After the randomization visit, a total of 4 follow-up visits were planned, the first the next day, the other three at two-week intervals.

Population under study

The study protocol included the enrollment of 20 healthy adult women evaluable for the primary endpoint. Any early drop-outs were to be replaced. However, the protocol provided for the interruption of recruitment as soon as this objective was reached.

Main inclusion and exclusion criteria

INCLUSION CRITERIA

1. Age between 18 and 50 years.
2. Caucasian race.
3. BMI (Body Mass Index) <30.
4. Blood pressure, measured in supine position after 5 minutes of rest, less than or equal to 90 mm / Hg and 140 mm / Hg for diastolic and systolic respectively.
5. Heart rate measured in supine position, after 5 minutes of rest, between 50 and 90 beats per minute.

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6. Signature of the informed consent form.

EXCLUSION CRITERIA

1. Pregnancy or breastfeeding in progress.
2. Changes (initiation or discontinuation) of estrogen-progestogen contraceptive use in the past 4 weeks.
3. Inability to adopt adequate contraception during the study phase.
4. Any disease or dysfunction, even asymptomatic, of endocrinological and thyroid importance in particular.
5. Any acute or chronic disease affecting any apparatus detectable by the anamnesis.
6. Any clinically significant abnormality detectable on physical examination.
7. Any clinically significant abnormalities detectable on the ECG.
8. Any clinically significant abnormalities in laboratory values.
9. History of allergy or intolerance to the products under study and / or to the excipients.
10. In the last 6 months, iodine-based treatments or therapies or use of iodine-containing drugs (eg amiodarone , Somatoline ®).
11. In the last 6 months, treatments with antithyroid drugs.
12. In the last 6 months, diagnostic investigations involving the use of tracers or contrast media containing iodine or its isotopes or treatments or therapies for chronic (eg diabetes, hypertension, etc.) or neoplastic diseases.
13. In the last 4 weeks, changes in the dietary regimen of foods containing iodine (eg iodized salt) or use of disinfectants (eg. Betadine), detergents or any product for systemic or topical use containing iodine, including mouthwashes (eg. Iodosan) , iodized toothpastes, vaginal douches, Lugol 's solutions .
14. In the last 2 weeks, treatments or therapies for acute diseases (antibiotics, NSAIDs), except hypnonductors or pain relievers as needed.
15. Abuse of alcohol (over 75 g / day of ethanol), xanthines (over 5 cups / day), tobacco (over 10 cigarettes / day) or use of psychotropic drugs (except for occasional use as hypno -inducers) or any drug.
16. Blood donations or bleeding within the previous three months or intentions to donate blood during the study and for the next 4 weeks.
17. Subjects who are unable, for linguistic or psychological reasons, to understand the information given to obtain consent or who refuse to give their consent in writing.
18. Other clinical study within four weeks prior to or during this study or intention to participate in an investigational drug study during this investigation.

The possible presence of cellulite was not an exclusion criterion but efficacy evaluations relating to this parameter were not envisaged.

Products under study, dosage, route of administration

There was only one study group, without a control group, treated with a formulation of Somatoline ® skin emulsion containing micronized thyroxine. The starting dose was two 10 g sachets of product per day (thyroxine 10 mg / escin 30 mg), one on each thigh, for the first two days, followed by a maintenance dose of half a sachet per thigh (5 g of product per thigh) until 4 weeks after application of the first dose.

The drug used in this trial was packaged using lot no. 1026, expiring 03/2015.

Statistical methodology

Statistical analysis was performed considering the following three populations:

a) " Intention To Treat " (ITT), defined as the group of randomized patients who have received at least one dose of study drug and have at least one evaluation at visit 2 (day 1 after inclusion in the study);
b) "Per - Protocol " (PP), defined as the set of ITT patients who do not have any "major" protocol violation and have at least completed the 28 day vision, including samples;
c) "Safety" (SS), defined as the group of randomized patients who received at least one dose of study drug.

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The results obtained were summarized by descriptive statistics (mean, standard deviation, median where appropriate, minimum and maximum) for continuous type variables or in frequency tables for categorical variables. The variables were analyzed by ANOVA. Where statistical tests were carried out, they were conducted at a significance level (level α) equal to 0.05.

SUMMARY

The primary objective, represented by the evaluation of changes with respect to the pre -treatment values in the systemic bioavailability of free l-thyroxine (FT_4) during and after the application of a new formulation of Somatoline ® according to the posology foreseen by the AIC, indicates that the product in question does not interfere with the plasma levels of the hormone neither in the short term, when applying the attack dose, nor in the long term at the end of the application cycle, nor two weeks after the completion of the treatment. The average value of FT4 in fact had, during the period considered, physiological fluctuations which were completely irrelevant, both from a clinical and a statistical point of view.

In full confirmation of this observation, during the study, there were no clinically or statistically relevant changes in the circulating levels of FT_3, TSH and rT_3.

Safety and tolerability

The drug was very well tolerated, with only one mild localized adverse event (folliculitis of the thighs) potentially attributable to the treatment in question. No systemic adverse events were observed.

Conclusions

The results of this study confirm that the systemic kinetics of the thyroid hormones evaluated here and the general safety and tolerability profile are not affected by the formulation changes made.

Report date

04/11/2011