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Clinical Study Report

Study Title:

Single-group, open study on the systemic bioavailability, safety and local tolerability of a new gel formulation of Somatoline® in 30 healthy women.

Study Code: Somagel

Sponsor code: Somagel

Test formulation:	Somatoline Gel
Reference formulation:	None.
Sponsor:	Società Italo Britannica, L. Manetti - H. Roberts & C. per Azioni, Via Baldanzese 177, I-50041 Calenzano (Firenze, Italy). Tel: (+39) 055 8835320
Development phase:	I

Clinical Study Report, Version and Date: Version 1.0 dated Friday, November 8, 2019

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Signature pages for clinical study report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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Versions history		
VERSION	DESCRIPTION	Date
1	Clinical Study Report	November 8, 2019

1 TITLE PAGE

STUDY TITLE: Single-group, open study on the systemic bioavailability, safety, local tolerability of a new gel formulation of Somatoline® in 30 healthy women.

EUDRACT NUMBER: 2018-002380-26

TEST DRUG: Somatoline Gel

STUDY TYPE: Open study.

SPONSORS: Società Italo Britannica, L. Manetti - H. Roberts & C. per Azioni, Via Baldanzese 177, I-50041 Calenzano (Firenze, Italy). Tel: (+39) 055 8835320

PROTOCOL: Somagel

CLINICAL PHASE: I

STUDY DATES: First patient in (FPI): 28-Jan-2019
Last patient out (LPO): 14-May-2019

INVESTIGATOR: Dr. Giovanni Gori

GCP STATEMENT: This study was performed in compliance with ICH Good Clinical Practices (GCP) including the archiving of essential documents.

DATE OF REPORT: 8 November 2019

2 SYNOPSIS

NAME OF SPONSOR: Società Italo Britannica, L. Manetti - H. Roberts & C. per Azioni. **NAME OF FINISHED PRODUCT:** Somatoline® Gel. **NAME OF ACTIVE INGREDIENT(S):** l-thyroxine and escin.		**INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Title of Study		Single-group, open study on the systemic bioavailability, safety, local tolerability of a new gel formulation of Somatoline® in 30 healthy women.	
Investigator(s)		Dr. Giovanni Gori	
Study centre(s)		Clinical Pharmacology Centre for Drug Experimentation, University Hospital, Via Roma, 67, Pisa (Italy).	
Publication		None	
Study period	From: FPI 28-Jan-2019 To: LPO 14-May-2019	Phase of development	I
Objectives		The primary objective was to assess the systemic bioavailability of l-thyroxine (l-T_4) in female subjects after repeated cutaneous application of a gel formulation of Somatoline® at the dosages recommended by the Summary of Product Characteristics (SmPC) of Somatoline® emulsion. The secondary objectives of the study were: • to assess the systemic bioavailability of reverse l-triiodothyronine (rT_3), T_3 and thyroid stimulating hormone (TSH), after repeated cutaneous application of a Somatoline® gel in female subjects; • to assess the local and systemic tolerability after repeated cutaneous application of a Somatoline® gel in female subjects	
Methodology		The study was run according to a single-group, open design.	
Number of subjects		Planned: 30 ITT Analysed: 30 PP Analysed: 30	
Diagnosis and main criteria for		**Inclusion criteria:** healthy women were enrolled in the study if they	

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inclusion	met all the following inclusion criteria: • *Sex and age*: Adult women aged between 18 and 50 years; • *Race*: Caucasian; • *Body mass index (BMI)*: 18.5 > BMI ≤ 30 kg/m^2; • *Vital signs*: systolic blood pressure (SBP) = 100-139 mmHg; diastolic blood pressure (DBP) = 50-89 mmHg; heart rate (HR) = 50-90 bpm, measured after 5 min of rest (sitting position); • *Electrocardiogram (ECG)*: no clinically relevant abnormalities at ECG (12 leads); • *Physical examination*: no clinically relevant abnormal physical findings; • *Laboratory analyses*: no clinically relevant abnormal laboratory values indicative of physical illness; • *Allergy*: no ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients or ß-lactam antibiotics; • *Medical history*: no history of anaphylaxis to drugs or allergic reactions in general, no relevant history of renal, hepatic, cardiovascular, respiratory, skin, haematological, endocrine, or neurological diseases that might interfere with the study aims; no history of gastric mucosal damages, no neoplasia, no medications during two weeks before the start of the study, including OTC; • *Participation in another experimental trial*: no participation in the evaluation of any experimental drug within 3 months prior to screening; • *Blood donors*: no blood donations during 3 months prior to this study; • *Drug or alcohol history*: no history of drug, alcohol (< 1 drink / day for females, defined according to USDA Dietary Guidelines 2000) or tobacco abuse (< 10 cigarettes/day); • *Pregnancy*: not pregnant or lactating; • *Contraception*: fertile women willing to use barrier	

contraceptive methods;

- *Subjects' capability*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigators and to comply with the requirements of the entire study;
- *ICF (informed consent form)*: signed written ICF prior to inclusion in the study;
- *Life-style:* Willingness of the subject to maintain a constant life-style during the period of the study.

Exclusion criteria: Women were excluded from the study if they met anyone of the following inclusion criteria:

- *Pregnancy*: pregnant or lactating women;
- *ECG*: clinically relevant abnormalities;
- *Physical findings*: clinically relevant abnormal physical findings which could interfere with the study objectives;
- *Laboratory analyses*: clinically relevant abnormal laboratory values indicative of physical illness;
- *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigators considered to potentially affect the outcome of the study;
- *Diseases*: relevant history of renal, hepatic, gastrointestinal (GI), cardiovascular, respiratory, skin, haematological, endocrine (in particular, thyroid), or neurological diseases, which may interfere with the study aims, history of gastric mucosal damages, neoplasia;
- *Contraceptive*: changes (early or suspension) of the use of contraceptive estrogen-progestin in the last 4 weeks, and inability to take adequate contraception during the study;
- *Medications and diet*: any medication, including OTC, was forbidden during the screening period. Moreover:
    - In the 6 months before screening, any treatment with

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	antithyroid drugs or any therapeutic use of iodine or iodine-containing medications (e.g., amiodarone, Somatoline®) was forbidden; ○ In the 6 months before screening, any diagnostic tests leading to the use of tracers, contrast agents containing iodine or iodine isotopes, was forbidden; ○ In the 4 weeks before screening, no changes in diet of foods containing iodine (e.g., iodized salt), or use disinfectants (e.g., betadine), detergents or any systemic or topical product containing iodine, including mouthwashes (e.g., Iodosan), toothpaste iodinated, douches, Lugol's solution, were allowed; ○ In the 4 weeks before screening, any use of food supplements and herbal medicines was allowed; ○ A daily intake of iodized salt < 1,100 µg/day. • *Investigative drug trials*: participation in the evaluation of any experimental drug within 3 months prior to the start of the study; • *Blood donation*: blood donations during the 3 months prior to this study; • *Drug, alcohol, tobacco*: history of drug, alcohol [> 1 drink/day for females defined according to USDA Dietary Guidelines 2000] or tobacco abuse (> 10 cigarettes/day).	
Test product, dose, and mode of administration	Somatoline® gel was applied daily at the dose of 10 grams on each thigh (20 grams per day in total) during the first 2 days, followed by 5 grams per thigh (10 grams per day in total) until the end of a 4-week period, starting from the day the first dose was applied. The subjects had to apply the product and then massage the skin of the entire thigh for several minutes until complete gel absorption.	
Reference product, dose, and mode of administration	None	
Duration of treatment	4 weeks (28 days).	
Criteria for evaluation	**Primary end-point**	

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	Blood samples for measurement of TSH concentrations were collected during the Screening (Day -15 to Day 0), Control 1 (Day 0 – Hour 5), Control 2 (Day 1), Control 3 (Day 14) and End of Treatment (EOT) (Day 28). The assessments were repeated at End of Study (EOS) visit (Day 42) after a 14-day follow-up, during which no treatment was performed. Apart from the Control 1 assessment, all blood samples were collected at the same day time, with a time window of ± 1 hour. **Safety assessment** Safety of the tested formulation has been evaluated based on the record of any adverse event (AE) and serious adverse event (SAE). Moreover, the local tolerability at the application site has been assessed by both the investigator (medical visit) and the subject (diary), throughout the entire study duration.	
Statistical methods	All continuous variables were summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation (s.d.), median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels were reported for all categorical measures. In general, all data were listed, sorted when appropriate by visit number, with the total population size relevant to that table, including any missing observations. ANOVA has been used to assess the systemic bioavailability of T_4 (primary endpoint) and rT_3, T_3, TSH, (secondary endpoints) after repeated cutaneous application of Somatoline® gel. Frequency tables have been provided for AEs and local tolerability, as well as for abnormalities detected with ECG, laboratory data and vital signs.	

SUMMARY CONCLUSIONS

DISPOSITION OF SUBJECTS. Based on a prior experience (Section 9.7.1), it was decided to enrol 30 subjects in order to have at least 26 subjects fully evaluated by assuming a dropout rate of 15%.

To achieve the goal, the experimental site has screened 34 volunteers, there were 4 volunteers who failed the screening, i.e. one volunteer who did fulfil the inclusion and exclusion criteria and three volunteers who withdrew their consent.

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A total of 30 subjects were therefore enrolled in the study, and all of them (100%) completed the study.

No volunteer dropped out.

DEMOGRAPHICS. All the volunteers were women and Caucasian according to the protocol. They aged between 18 to 47 years (mean ± s.d.: 33.3 ± 8.61 years), with a BMI ranging between 18.9 and 26.8 kg/m², as per the inclusion criteria (mean ± s.d.: 22.4 ± 2.2). The height ranged between 159 and 176 cm (mean ± s.d.: 165.1 ± 4.90 cm), and the weight ranged between 50 and 74 kg (mean ± s.d.: 61.2 ± 6.3 kg).

All pregnancy tests were negative, and all women used barrier contraceptive methods. All drugs screening tests were negative, and the use of alcohol and nicotine was within the inclusion criteria.

SYSTEMIC BIOAVAILABILITY RESULTS. After a 28-day cutaneous application of Somatoline® gel the plasma concentrations of T_4 always remained within the normal range and they showed no clinically relevant changes across the different times from Baseline (1.13 ± 0.15 ng/dL) to EOT (1.11 ± 0.13 ng/dL)

The plasma concentration of T_3 and TSH were unchanged when the mean values at Baseline (3.83 ± 0.52 ng/dL and 1.54 ± 0.69 mUI/L, respectively) were compared with the values at the EOT (3.80 ± 0.40 ng/dL and 1.85 ± 1.00 mUI/L, respectively) while a T_3 and TSH blood level reduction was observed at the Control 1 (Day 0 – 5 hours). No statistically (ANOVA analysis) significant difference was observed at any time.

SAFETY RESULTS. All the 30 subjects enrolled into the study correctly completed the required 28 days of treatment; in these subjects the exposure to cutaneously applied Somatoline® gel was 20 grams/daily during the first 2 days, followed by 10 grams/daily for the next 26 days. The total exposure was therefore 300 grams of Somatoline® gel / 28 days, corresponding to T_4 3 grams / 28 days and escin 9 grams / 28 days.

No deaths and no SAEs were reported overall the study period, Eight (8) subjects (26.7%) reported eighteen (18) AEs during treatment period and one (1) during follow up. "Headache" was the mainly reported AE (5 subjects [16.7%]).

"Erythema" (expected) and "pruritus" (unexpected) were the only AEs considered related by the investigator.

There was no statistically significant variation from baseline in vital signs.

No clinically relevant abnormality over time were observed for the clinical laboratory results, 12-lead ECGs or physical examination findings.

As for the local tolerability, the Investigator reported no signs of "redness" or "swelling"; one (1) case of "itching" was reported by the Investigator; three (3) mild redness and two (2) mild itching were self-reported by the subjects.

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CONCLUSIONS. The study has been aimed at investigating the bioavailability of l-T4 (primary objective) after a repeated cutaneous application of Somatoline® gel.

Moreover, the plasma levels of T3, rT3 and TSH were also evaluated with the rationale to rule out a putative transcutaneous absorption of l-T4, as active ingredient of Somatoline® gel, and its interference on systemic thyroid homeostasis aftert a repeated cutaneous application of Somatoline® gel secondary, the local and systemic tolerability of Somatoline® gel were explored.

Blood levels of T4 and T3, rT3 or TSH were measured during and after the Somatoline® gel administration.

In compliance with the recommended dosage as per SmPC of Somatoline® emulsion , the study has been performed with a cutaneous application of Somatoline® gel for 28 consecutive days of treatment (20 grams/day on the first two days followed by 10 grams/day for the next 26 days), followed by a 14-day follow-up period.

30 Caucasian healthy women were enrolled in the study.

Compliance to treatment schedule was 99.5% and there was no clinically relevant protocol deviation (PD).

Blood samples for T_4, T_3, rT_3 and TSH levels were drawn at Baseline, 5 and 24 hours after the first application and thereafter on Days 14, 28 and 42.

The plasma concentrations of T_4 were not affected by the application of Somatoline® gel, at any time during the study.

Not clinically relevant changes were observed in the T_3 and TSH plasma concentrations, which showed a slight decrease five hours after the first Somatoline® gel application.

No other changes were observed in the T_3 and TSH concentrations throughout during the remaining part of the studyboth at the medium (Control 2, EoT) and long (EoS) term.

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No SAE occurred during the study and only two AEs (erythema and pruritus) were reported and considered possibly related to the treatment by the investigator.

In conclusion the treatment resulted safe and well tolerated

3 TABLE OF CONTENTS

1 TITLE PAGE 4

2 SYNOPSIS 5

3 TABLE OF CONTENTS 12

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 15

5 ETHICS 17

5.1 COMPETENT AUTHORITY APPROVAL 17
5.2 INDEPENDENT ETHICS COMMITTEE APPROVAL 17
5.3 ETHICAL CONDUCT OF THE STUDY 17
5.4 SUBJECTS' INFORMATION AND CONSENT 17

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE 17

7 INTRODUCTION 18

7.1 BACKGROUND INFORMATION 18
7.2 RATIONALE OF THE STUDY 21

8 STUDY OBJECTIVES 22

8.1 PRIMARY OBJECTIVE 22
8.2 SECONDARY OBJECTIVE 22
8.3 END POINTS 22

9 INVESTIGATIONAL PLAN 22

9.1 OVERALL STUDY DESIGN AND PLAN 22
9.1.1 Study Timing 24
9.1.2 Study Location 24
9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS 24
9.3 SELECTION OF STUDY POPULATION 25
9.3.1 Inclusion Criteria 25
9.3.2 Exclusion Criteria 26
9.3.3 Removal of Subjects from Therapy or Assessment 27
9.4 TREATMENT 27
9.4.1 Treatments Administered 27
9.4.1.1 Test formulation 27
9.4.1.2 Reference formulation 28
9.4.2 Methods of Assigning Subjects to Treatment Groups 28
9.4.3 Selection of Doses in the Study 28
9.4.4 Selection and Timing of Dose for Each Subject 28
9.4.5 Blinding 28
9.4.6 Prior and Concomitant Therapies 28
9.4.7 Treatment Compliance 29
9.5 SYSTEMIC BIOAVAILABILITY AND SAFETY VARIABLES 29
9.5.1 Systemic bioavailability and Safety Measurements Assessed 29
9.5.1.1 Primary variables 29
9.5.1.2 Drug Concentration Measurements 29
9.5.1.3 Secondary variables 29

9.6 DATA QUALITY ASSURANCE 30
9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE 30
9.7.1 Determination of Sample Size 30
9.7.2 Statistical and Analytical Plans 31
9.7.3 Analysis on Demographic Characteristics 32
9.7.4 Physical examination, vital signs and ECGs 32
9.7.5 Analysis of bioavailability 33
9.7.6 Analysis on Safety and Local Tolerability 34
9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES 34
9.8.1 Protocol Amendments 34

10 STUDY POPULATION 34

10.1 DISPOSITION OF SUBJECTS 34
10.2 PROTOCOL DEVIATIONS 35

11 RESULTS 35

11.1 DATA SETS ANALYSED 35
11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 36
11.2.1 Demographics 36
11.2.2 Concomitant Illnesses 36
11.2.3 Concomitant Medications 36
11.3 MEASUREMENTS OF TREATMENT COMPLIANCE 36
11.4 SYSTEMIC BIOAVAILABILITY RESULTS AND TABULATIONS OF INDIVIDUAL SUBJECTS DATA 37
11.4.1 Plasma Concentrations 37
11.4.2 Statistical / Analytical Issues 38
11.4.2.1 Adjustments for Covariates 38
11.4.2.2 Handling of Dropouts or Missing Data 38
11.4.2.3 Interim Analyses and Data Monitoring 38
11.4.2.4 Multicenter Studies 38
11.4.2.5 Multiple Comparison / Multiplicity 38
11.4.2.6 Use of an "Efficacy Subset" of subjects 39
11.4.2.7 Active-Control Studies Intended to Show Equivalence 39
11.4.2.8 Examination of Subgroups 39
11.4.3 Tabulation of Individual Response Data 39
11.4.4 Drug Dose, Drug Concentration, and Relationship to Response 39
11.4.5 Drug-Drug and Drug-Disease Interactions 39
11.4.5 By-Patient Displays 39
11.5 SYSTEMIC BIOAVAILABILITY CONCLUSIONS 39

12 SAFETY EVALUATION 40

12.1 EXTENT OF EXPOSURE 40
12.2 ADVERSE EVENTS 40
12.2.1 BRIEF SUMMARY OF ADVERSE EVENTS 40
12.2.2 Display of Adverse Events 40
12.2.3 Analysis of Adverse Events 40
12.2.4 Listing of Adverse Events by Patient 41
12.3 LOCAL TOLERABILITY 41
12.4 DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS 42
12.5 CLINICAL LABORATORY EVALUATION 42

12.5.1 Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal Laboratory Value (14.3.4) 42
12.4 EVALUATION OF EACH LABORATORY PARAMETER 42
12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY 42
12.6 SAFETY CONCLUSIONS 43
13 DISCUSSION AND OVERALL CONCLUSIONS **43**
14 TABLES, FIGURES AND GRAPHS **45**
***14.1* DEMOGRAPHIC DATA** 49
***14.2* SYSTEMIC BIOAVAILABILITY DATA** 50
***14.3* SAFETY DATA** 54
15 REFERENCE LIST 56

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
BMI	Body Mass Index
C.I.	Confidence Interval
CR	Clinically relevant
CRF	Case Report Form
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EOS	End of Study visit
EOT	End of Treatment visit
FPI	First Patient In
GAGS	Glycosaminoglycans
GCP	Good Clinical Practices
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ITT	Intent to Treat
LPO	Last Patient Out
N	Number of cases
NCR	Non clinically relevant
OTC	Over the Counter
PD	Protocol deviation
PI	Principal Investigator
PIL	Patient Information Leaflet
PP	Per Protocol
PT	Preferred Term
PSUR	Periodic Safety Update Report
RF	Respiratory frequency
SAE	Serious adverse event
SAP	Statistical Analysis Protocol
SBP	Systolic Blood Pressure

s.d.	Standard deviation
SmPC	Summary of Product Characteristics
SOC	
rT_3	reverse l-triiodothyronine
T_3	l-triiodothyronine
T_4	l-thyroxine
TSH	Thyroid Stimulating Hormone

5 ETHICS

5.1 COMPETENT AUTHORITY APPROVAL

The study was performed in compliance with the requirements of the Italian Competent Authority (Agenzia Italiana del Farmaco, AIFA) (Appendix 16.1.4). The study was granted with a full regulatory approval on 12-Sep-2018 (AIFA) and on 13 Sep 2018 (EC) and the study was identified with the EudraCT number 2018-002380-26.

5.2 INDEPENDENT ETHICS COMMITTEE APPROVAL

The study protocol and any amendment (Appendix 16.1.1), and the Patient Information Leaflet (PIL) and Informed Consent Form (ICF) were reviewed and approved by the competent Independent Ethics Committees (IEC) as detailed below (Appendix 16.1.3).

5.3 ETHICAL CONDUCT OF THE STUDY

The trial has been performed in accordance with the current version of the declaration of Helsinki (last version 7, 2013) and in agreement with the International Conference on Harmonization (ICH) guidelines on Good Clinical Practices (GCP).

5.4 SUBJECTS' INFORMATION AND CONSENT

All the subjects enrolled in the trial have signed an ICF to participate in the study prior to being screened (Appendix 16.1.3).

The PIL detailed the procedures involved in the study (aims, methodology. potential risks, anticipated benefits) and the Principal Investigator (PI) explained these to each subject in further details. The subjects were then allowed to ask any clarification or further information, and they had enough time to believe about the provided information before signing and dating the ICF to demonstrate that they fully understood the information, and willingly volunteered to participate in the study. The subjects were given a copy of the ICF for their information, while the original ICF copy was filed in the Investigator's Site File (ISF) at the research center.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Details on the study personnel involved in the study are given in the Appendix 16.1.5.

7 INTRODUCTION

7.1 BACKGROUND INFORMATION

The "edematous fibrosclerotic panniculopathy" - more commonly known as "cellulite" - is a localized metabolic disorder of the subcutaneous layer of skin, the dermis, and its small blood vessels. Over years, these vessels become compressed, resulting in inflammation, poor lymph drainage, proliferation of fibrous tissue, tissue damage, unevenness of the skin thickness, and the protrusion (herniation) of fat through layers of the skin. The primary areas involved - the thighs, abdomen, and buttocks - acquire the uneven, dimpled, and textured skin of an orange ("peau d'orange") or the lumpiness of cottage cheese. Cellulite is common and found in from 85 to 98% of post-adolescent females (though more often in Caucasian than Asian or Black women). It is rarely seen in males but is more common in males with androgen-deficient states, such as Klinefelter's syndrome, hypogonadism, post-castration states and in those subjects receiving estrogen therapy for prostate cancer.

The causes of cellulite include changes in metabolism, physiology, dieting too hard or too much, sex-specific dimorphic skin architecture, alteration of connective tissue structure, hormonal factors, genetic factors, microcirculatory system, extracellular matrix, and subtle inflammatory alterations (Avram 2004; Pavicic et al. 2006). As mentioned above, cellulite is not a static condition. If left untreated, it can get worse. Early intervention may help reduce or even prevent its insidious progression. Indeed, the following stages occur during cellulite formation (Marenus, 1997):

- STAGE ONE: it involves a deterioration of the skin dermis, whereby the integrity of the blood vessels and capillaries that create a complex transport network throughout the skin slowly begins to break down. Similarly, the upper region of the dermis begins to lose some of its capillary network. Fat cells, housed within the freestanding fat cell chambers, begin to engorge with lipids, often swelling 2-3 times their original size. Fat cell clumping may commence at this stage as well. Fluid begins to accumulate in the tissue, most likely due to a breakdown in the capillary system. Projections of fat begin to occur in the dermis and there is an increase in glycosaminoglycans (GAGS), which may account for the enhanced ability for tissues to retain excess water;

  Visible signs: The pre-cellulite stage when skin will show no real visible signs, although bruises and cuts may be slow to heal. When pinched gently between the forefinger and thumb, the skin shows a slight 'orange-peel' effect'.

- STAGE TWO: dermal deterioration increases, and the microcirculatory system continues to decline. Fat cells engorge further, and clumping is more pronounced, so that the compression of the blood vessels keeps on increasing. The appearance of gaps in the dermis, which may be the result of the normal inflammatory process, is common. Such process activates specific enzymes such as collagenase and elastase, creating an available path for immune cells to migrate to the site of inflammation. Fluids continue to accumulate. At this stage, "orange peel" skin becomes to be evident;

Visible signs: Close examination of the skin reveals broken veins and skin discoloration. Bruises may appear after the smallest of knocks. The skin feels thicker and slightly tender if pinched gently between the forefingers and thumb. You can also see definite 'orange-peel effect.

- STAGE THREE: the microcirculatory system continues to deteriorate, slowing metabolism in the cells of the dermis. Both protein synthesis and the repair process are reduced drastically, which may contribute to a thinning of the dermal layer. Protein deposits begin to form around fat cell clusters. Pinching the skin between finger and thumb at this stage demonstrates a definite "orange peel" effect;

  Visible signs: Without pinching, the skin appears tethered and puckered- this is known as 'mattress skin'. It is obviously swollen, defining the appearance of the sweat glands and hair follicles. Fluid retention is now a permanent feature, giving the skin the classical orange peel effect. Bruising occurs spontaneously. The skin feels cold to the touch. Broken veins may be present, and if so, these will be large and often clearly visible below the cellulite areas.

- STAGE FOUR, hard nodules are evident in the dermal region. These are comprised of fat cell clumps encased in a hardened protein shell.

  Visible signs: The skin is becoming deprived of oxygen and nutrients, it now bruises easily, is swollen and is becoming tender to the touch because of the fluid causing pressure in the tissues. The skin now feels cold to the touch.

- STAGE FIVE, the blood has been redirected around the effected tissue.

  Visible signs: all of the previous stages are visible, but now with the buildup of pressure the blood is forced through the area to respond to metabolic toxins. These cause hot islands amongst the otherwise cold tissue, making the skin appear blotchy, with red-hot islands.

- STAGE SIX, the presence of steatomes and the distorted silhouette show the cellulite to be well established. Fat cannot be naturally eliminated from the cells because of the poor blood circulation. However, fat continues to be stored in the cells because of the preponderance of fat-storing receptors on the surface of the cells.

  Visible signs: the body's silhouette begins to disfigure, forming bulky solid masses of lumps and bumps. All of the previous stages are present, but the condition can continue to build, due to the body's natural fat storing receptors. The fibres become thicker and more numerous, forming huge honeycombs of fat, fluid and fibre known as steatomes.

There are diagnostic tests available (e.g., ultrasound) that can detect the presence of cellulite and determine the extent of the condition; however, these tests are usually unnecessary. Cellulite can be diagnosed by pinching or rolling the skin in the affected area.

Somatoline® is a medicinal product that has been authorized for marketing in Italy since November 1973 for the treatment of localized adiposity accompanied by cellulite. The product

is today manufactured as cutaneous emulsion containing l-thyroxine (l-T_4) at the concentration of 0.1% (i.e., 100 mg per 100 grams of emulsion) and escin at the concentration of 0.3% (i.e., 300 mg per 100 grams of emulsion); the product is sold as 10-g sachets for cutaneous application.

The active ingredients of Somatoline® - -thyroxine and escin - exert their activity mainly on adipose tissue, activating the process of hydrolysis and mobilization of triglycerides and fatty acids, and developing an inhibitory action on the synthesis of lipids. They act also on the permeability of the capillaries, exerting anti-edema action and removal of stagnant liquids in the tissues, playing a mobilizing effect at the tissue level of saline water collected, frequently found in the tissues affected by cellulite.

Somatoline® has been reported to show a consistent tolerability across the years.

Since 1995 up to December 2016, it has been estimated that 8.359.197 packs of Somatoline® have been sold, which are equivalent to 208.757.975 doses (1 dose corresponding to 1 sachet or to 2 sprays) covering about 5.218.949 cycles of treatment (40 consecutive days, using 1 dose of 10 g per day). Thus, assuming that to each cycle corresponds a subject, it is estimated that a total number of about 5.218.949 subjects have been exposed to Somatoline®. During this long period, the evaluation of the cumulative safety data and the benefit-risk analysis have confirmed the favorable safety profile of the medicinal product (PSUR, 2017).

The safety of use of Somatoline® is supported by bioavailability studies performed after cutaneous administration, which document the lack of any significant systemic absorption of the active compounds. In particular, Buraglio (1997) demonstrated that topical application of l-T_4 did not affect physiological levels of pituitary and thyroid hormones, finding which was further clinically confirmed by Galbiati et al. (2002) and more recently by in vitro studies performed by Padula et al. (2008).

More recently, Certan et al. (2013) have assessed the systemic effects of a cycle of treatment with the Somatoline® emulsion in healthy women based on changes in bioavailability of free l-T_4, free l-T_3, reverse l-T_3 (rT_3) and thyroid stimulating hormone (TSH). The study enrolled 20 healthy adult women with a body mass index (BMI) lower than 30, not exposed to iodine-containing products. The study called for 28 consecutive days of treatment with Somatoline® followed by a 14-day follow-up period. Blood samples for l-T_4, T_3 and TSH levels were drawn at baseline, 5 and 24 hours after the first application, and thereafter on days 14, 28 and 42. Levels of rT_3 were measured during the first 24 hours post-application.

Subject mean age was 40.1 ± 8.0 years and BMI ranged between 19.1 and 29.8. Levels of l-T_4 always remained within normal range and did not change in a clinically relevant way from baseline (11 ± 1.2 pg/dL), with maximum mean change from pre-treatment values of 0.4 pg/mL ($p = 0.87$). Likewise, T_3 and TSH levels did not change significantly from baseline (3 ± 0.4 pg/dL and 1.8 ± 0.9 μU/mL, respectively). Levels of rT_3 behaved in a similar way, with modest changes from baseline.

Local tolerability was defined "excellent" for 19 out of 20 women (95%) and "moderate" in one subject who experienced the onset of folliculitis, for which causal correlation with the

treatment was considered "possible".

Thus, once Somatoline® is used under the recommended modes of use, the application of the product does not affect the plasma concentrations of T_4, T_3, rT_3 and TSH, either in the short-term application or and a prolonged 28-day use (Certan et al. 2013).

7.2 RATIONALE OF THE STUDY

Somatoline® has been actually developed in the pharmaceutical form of gel. The quali- and quantitative composition of Somatoline® gel is reported in the following:

Cod. MP	MATERIE PRIME	%
R162008	Acqua demi.	89,42
R104812	L-Tiroxina micronizzata	0,10
R096181	Escina	0,30
R094693	Gomma Xantana	0,20
-	Carbopol 980 (Lubrizol)	0,40
-	Trietanolammina (Carlo Erba)	0,38
R010261	Sorbitolo sol. 70%	3,00
R053451	Imidazolidinyl urea	0,30
-	Alcol Etilico 96 (Distilleria Scardina)	5,00
R170821	Profumo Rose 10138D	0,10
-	Fenossietanolo (Faravelli)	0,80
		100

SOMATOLINE GEL	
acqua	89,40g
alcol etilico 96%	5,00g
sorbitolo	3,00g
fenossietanolo	0,80g
carbopol 980 NF	0,40g
trietanolammina	0,38g
imidazolidinyl urea	0,30g
escina	0,30g
gomma xantan	0,20g
levotiroxina	0,10g
profumo	0,10g
TOT	100,00 g

Somatoline® gel ingredients

This study has been aimed to investigate the safety of the gel formulation, by assessing the bioavailability of T_4 and the behavior of the plasma concentrations of T_4, T_3, rT_3 and TSH after a 28-day cutaneous application of Somatoline® gel.

The systemic and local safety of use of Somatoline® emulsion has been documented by biochemical and pharmacological evidences, as well as by the previously performed studies of bioavailability, which documented that no clinically relevant amounts of T_4 are systemically absorbed after cutaneous repeated application (Somatoline® Investigator's Brochure v. 2 of 3rd July 2018).

No significant cutaneous absorption of T_4 was therefore expected with Somatoline® gel, thus the risks for subjects who accepted to participate in this study were estimated to be identical to those related to current use of Somatoline® emulsion in the standard daily body care.

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of the study was to assess the systemic bioavailability of l-T_4 in female subjects with local cellulitis after repeated cutaneous of Somatoline® gel according to the proposed posology as per Investigator's Brochure (Somatoline® Investigator's Brochure v. 2 of 3rd July 2018).

8.2 SECONDARY OBJECTIVE

The secondary objectives of the study were:

- to assess the systemic bioavailability of T_3, rT_3, and TSH, after repeated cutaneous application of Somatoline® gel in female subjects with local cellulitis;
- to assess the local and systemic tolerability after repeated cutaneous application of Somatoline® gel in female subjects with local cellulitis.

8.3 END POINTS

The primary endpoint was to compare the pre-treatment plasma concentrations of l-T_4 with those observed 24 hours, 14 days and 28 days after a cutaneous repeated application of Somatoline® gel, and 14 days after the last application of the gel (Day 42 of follow-up).

The secondary endpoint was to compare the plasma concentrations of T_3, rT_3, and TSH with those observed 24 hours, 14 days and 28 days after a cutaneous repeated application of Somatoline® gel, and 14 days after the last application of the gel (Day 42 of follow-up).

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

The study was run according to a single-group, open design.

Briefly, a group of 30 Caucasian healthy woman, aged between 18 and 50 years, was selected for the participation into the study, during a Screening period which could not last more than 15 days (Day -15 to Day 0).

Women were early informed about the purposes of the study and the risks related to the study participation. If they agree to participate, they were consented with the most recently IEC-approved ICF, and then evaluated for their compliance to the inclusion and exclusion criteria. Once the eligibility of women had been confirmed, they were assessed for plasma concentrations of T_4, T_3, rT_3 and TSH.

No dietary changes of iodine-containing food or changes in the use of iodine-containing disinfectants, detergents or mouthwash products were allowed during the study. A maximal

daily intake of iodized salt of 1,100 µg/day was allowed. In order to check the compliance of subjects with this requirement, the concentrations of iodide in the urine were assessed at the Screening and End of Study (EOS) visit.

At Baseline (Day 0), after a medical visit has been reconfirmed the eligibility criteria and a negative pregnancy test has been obtained, the women were assessed again for plasma concentrations of T_4, T_3, rT_3 and TSH.

After these examinations, women were instructed to apply Somatoline® 10 grams gel (equivalent to l-T_4 10 mg and escin 30 mg) on each thigh per day during the first 2 days (20 grams per day in total, equivalent to l-T_4 20 mg and escin 60 mg), followed by 5 grams per thigh (10 grams per day in total, equivalent to l-T_4 10 mg and escin 30 mg) until the end of a 4-week period starting from the day the first dose was applied. The subjects had to apply the product and then massage the skin of the entire thigh for several minutes until complete absorption of the gel.

Blood samples for measurement of T_4, T_3, rT_3 and TSH levels were repeated at Control 1 (Day 0, 5 hours after the first application of Somatoline®) and Control 2 (Day 1, 24 hours after the first application of Somatoline®), and then again on Day 14 and Day 28 (End of Treatment [EOT] visit).

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory frequency and body temperature) were assessed at each visit. A full medical examination was repeated at the EOS.

In order to assess the systemic tolerability of a treatment with Somatoline® gel, on Day 0, Day 1, Day 14 and Day 28, EOT and EOS (Follow-up), women were asked for any AE or any issue observed during the treatment, and the bilateral sites of drug application were inspected for any local reaction (erythema, swelling and itching), which were scored. Moreover, a diary was given to the patients at Day 0 and the patients were asked to daily score any sign of erythema, swelling and itching, at the application site.

Finally, a 12-lead ECG was run at the Screening and repeated on Day 0 (5 hours after the first Somatoline® application), on EOT and EOS, to assess any potential systemic absorption of T_4 and related effects on cardiac activity.

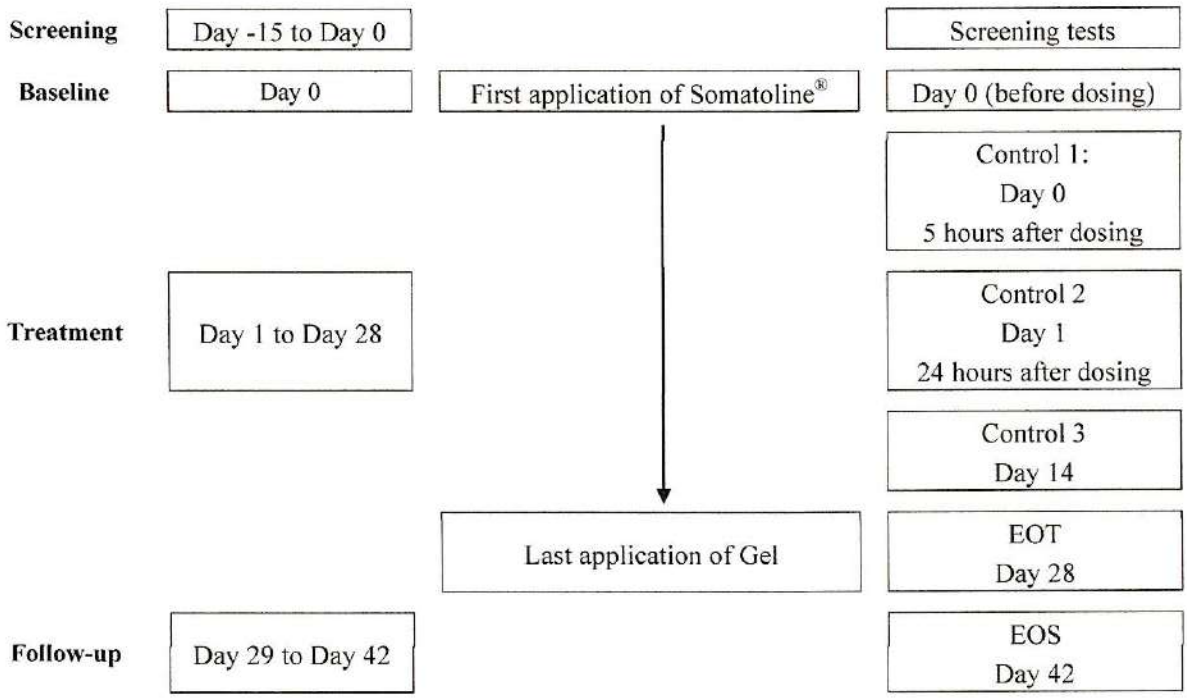
After the EOT (Day 28), women were followed for additional 14 days. During the follow-up period, no treatment with Somatoline® was allowed.

On Day 42 (EOS), blood samples for measurement of T_4, rT_3, T_3 and TSH levels were drawn.

On the same Day, women were asked for any AE or any issue observed during the treatment, and the bilateral sites of drug application were inspected for any local reaction, which were scored.

An overview of the overall study design is provided in the next flow-chart.

STUDY FLOW CHART



9.1.1 Study Timing

The Table 1 shows the activities that were performed during the study, visit by visit. The final analysis was performed after database lock on data transferred from SAS-Pheedlt (eCRF) and after the finalization and approval of the SAP document.

9.1.2 Study Location

The study was run at the Clinical Pharmacology Centre for Drug Experimentation, University Hospital, Via Roma, 67, Pisa (Italy).

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The study was aimed to gathering preliminary information on the systemic absorption of T_4 after cutaneous application of Somatoline® gel. Thus, there was no control group and the study has been run in open conditions.

9.3 SELECTION OF STUDY POPULATION

Healthy Caucasian woman, aged between 18 and 50 years, were enrolled in the study.

9.3.1 Inclusion Criteria

Healthy women were enrolled in the study if they met all these inclusion criteria:

- *Sex and age*: Adult women aged between 18 and 50 years;
- *Race*: Caucasian;
- *Body mass index* (BMI): 18.5 > BMI < 30 kg/m2;
- *Vital signs*: systolic blood pressure (SBP) = 100-139 mmHg; diastolic blood pressure (DBP) = 50-89 mmHg; heart rate (HR) = 50-90 bpm, measured after 5 min of rest (sitting position);
- *Electrocardiogram* (ECG): no clinically relevant abnormalities at ECG (12 leads);
- *Physical examination*: no clinically relevant abnormal physical findings;
- *Laboratory analyses*: no clinically relevant abnormal laboratory values indicative of physical illness;
- *Allergy*: no ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients or ß lactam antibiotics;
- *Medical history*: no history of anaphylaxis to drugs or allergic reactions in general, no relevant history of renal, hepatic, cardiovascular, respiratory, skin, hematological, endocrine, or neurological diseases that may interfere with the study aims, no history of gastric mucosal damages, no neoplasia, no medications during two weeks before the study starting, including OTC ("over the counter");
- *Participation in another experimental trial*: no participation in the evaluation of any experimental drug within 3 months prior to screening;
- *Blood donors*: no blood donations during 3 months prior to this study;
- *Drug or alcohol history*: no history of drug, alcohol (< 1 drink/day for females, defined according to USDA Dietary Guidelines 2000) or tobacco abuse (< 10 cigarettes/day);
- *Pregnancy*: not pregnant or lactating (for female healthy subjects);
- *Contraception:* fertile women willing to use barrier contraceptive methods;
- *Subjects' capability*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study;
- *ICF*: signed written ICF prior to inclusion in the study;

- *Lifestyle*: Willingness of the subject to maintain a constant lifestyle during the period of the study.

9.3.2 Exclusion Criteria

Women were excluded from the study if they met anyone of these inclusion criteria:

- *Pregnancy*: pregnant or lactating women;
- *ECG*: clinically relevant abnormalities;
- *Physical findings*: clinically relevant abnormal physical findings which could interfere with the study objectives;
- *Laboratory analyses*: clinically relevant abnormal laboratory values indicative of physical illness;
- *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considered to potentially affect the outcome of the study;
- *Diseases*: relevant history of renal, hepatic, gastrointestinal (GI), cardiovascular, respiratory, skin, hematological, endocrine (in particular, thyroid), or neurological diseases, which may interfere with the study aims, history of gastric mucosal damages, neoplasia;
- *Contraceptive*: changes (early or suspension) of the use of contraceptive estrogen-progestin in the last 4 weeks, and inability to take adequate contraception during the study;
- *Medications and diet*: any medication, including OTC, was forbidden during the screening period. Moreover:
    - In the 6 months before screening, any treatment with antithyroid drugs or any therapeutic use of iodine or iodine-containing medications (e.g., amiodarone, Somatoline®) was forbidden;
    - In the 6 months before screening, any diagnostic tests that led to the use of tracers, contrast agents containing iodine or iodine isotopes, was forbidden;
    - In the 4 weeks before screening, no changes was allowed in diet of foods containing iodine (e.g., iodized salt), or use disinfectants (e.g., betadine), detergents or any systemic or topical product containing iodine, including mouthwashes (e.g., Iodosan), toothpaste iodinated, douches, Lugol's solution;
    - In the 4 weeks before screening, any use of food supplements and herbal medicines was forbidden;

- A daily intake of iodized salt < 1,100 µg/day was allowed.

- *Investigative drug trials*: participation in the evaluation of any experimental drug within 3 months prior to the start of the study;
- *Blood donation*: blood donations during the 3 months prior to this study;
- *Drug, alcohol, tobacco*: history of drug, alcohol [> 1 drink/day for females defined according to USDA Dietary Guidelines 2000] or tobacco abuse (> 10 cigarettes/day).

9.3.3 Removal of Subjects from Therapy or Assessment

Subjects were free to withdraw from the study at any time without providing any reason. Subjects were advised that if they request to withdraw from the study at any time during the trial, this has no negative consequences.

The PI could also withdraw subjects from the trial if he deemed it appropriate for safety or ethical reasons, or if he believed that the continuation of the study would have been detrimental to the subjects' well-being.

Subjects could be withdrawn also for the following reasons:

- if an AE - including a concomitant illness - developed and considered by the Investigator incompatible with the study continuation;
- if the administration of a drug which is not allowed by the exclusion criteria, became necessary;
- failure to comply with requirements of the protocol.

No subject interrupted the treatment or was withdrawn from the study for any reason.

9.4 TREATMENT

9.4.1 Treatments Administered

9.4.1.1 Test formulation

Somatoline® gel was the investigational medicinal product (IMP) to be used in the trial. The study medication characteristics are reported in Table 2.

The women enrolled into the study were instructed to apply Somatoline® 10 grams gel – corresponding to l-T_4 10 mg and escin 30 mg - on each thigh per day during the first 2 days (20 grams per day in total, corresponding to l-T_4 20 mg and escin 60 mg), followed by 5 grams per thigh (10 grams per day in total, corresponding to l-T_4 10 mg and escin 30 mg) until the end of a 4-week period starting from the day the first dose was applied.

The women were instructed and required to apply the product on the skin and then to massage the skin of the entire thigh for several minutes until complete percutaneous absorption. The

dosage and administration way of Somatoline® gel were consistent with the recommendations of the Somatoline® Investigator's Brochure. 2 dated 3rd July 2018.

9.4.1.2 Reference formulation

No control group and no reference formulation were used in the clinical trial.

9.4.2 Methods of Assigning Subjects to Treatment Groups

The study was open with a single-group and, therefore, no randomization procedure was in place.

9.4.3 Selection of Doses in the Study

The study was aimed to investigate the percutaneous absorption of T_4 during a standard use of Somatoline® gel. Therefore, the dosage and administration way of Somatoline® gel were consistent with those recommended by the Somatoline® Investigator's Brochure. 2 dated 3rd July 2018.

9.4.4 Selection and Timing of Dose for Each Subject

Somatoline® was applied once daily for 28 consecutive days. The timing of dose is consistent with the recommendations of the Somatoline® Investigator's Brochure. 2 dated 3rd July 2018 and with expected use of the product by women with local cellulitis in the standard-of-care practice.

9.4.5 Blinding

The study was open.

9.4.6 Prior and Concomitant Therapies

No dietary changes of iodine-containing food or changes in the use of iodine-containing disinfectants, detergents or mouthwash products were allowed during the study. A maximum daily intake of iodized salt < 1,100 µg/day was allowed during the study. In order to check the compliance of the subjects with this requirement, the concentrations of iodide in the urine will be assessed at the Screening and EOS.

There was no other restriction in prior and/or concomitant therapies, which were anyway recorded in the subjects' medical charts. Notwithstanding, subjects could undertake other medical treatments only under approval of the Investigator, except in case of emergencies.

9.4.7 Treatment Compliance

At Baseline, Somatoline® gel was cutaneously applied by the subjects at the Site under the Investigator's instructions; thus, the treatment compliance was directly checked by the Clinical staff. Later on, Somatoline® gel was applied by subjects at home, once daily for 27 consecutive days.

In order to check the subjects' compliance with treatment, the subjects were asked to fill a daily diary and to return the filled diary at the EOT visit. In this diary, the subjects declared if they had applied Somatoline® gel on the cutaneous surface of the right and left thighs. Moreover, the subjects were asked to retain the used drug and bring it back to the Site at the subsequent visit.

All the 30 female subjects correctly completed all 28 days of treatment, with the exception of two (2) subjects (No. 2 and 24) who forgot to apply Somatoline® gel for only one day (1), and one (1) subject (N ° 27) for two (2) days (Tables 14.5.1.X). In total, four (4) days of non-treatment on 840 days of treatment (30 subjects x 28 days), equal to 0.5% that is 99.5% of compliance as reported by the subjects in their diary.

9.5 SYSTEMIC BIOAVAILABILITY AND SAFETY VARIABLES

9.5.1 Systemic bioavailability and Safety Measurements Assessed

The Table 3 shows the systemic bioavailability and safety measurements that were assessed during the study, visit by visit.

9.5.1.1 Primary variables

The primary objective of the study was to assess the systemic bioavailability of l-T_4 after a repeated cutaneous application of Somatoline® gel; thus, the plasma concentrations of T_4 were assessed at Baseline and each control time. The mean plasma concentrations of T_4 and the changes from baseline at each control time were assessed by means of ANOVA for statistical significance.

9.5.1.2 Drug Concentration Measurements

In addition to the assessment of T_4, rT_3, T_3 and TSH, no other drug concentration measurement was performed.

9.5.1.3 Secondary variables

In order to investigate a percutaneous absorption of l-T_4 after a repeated cutaneous application of Somatoline® gel, the plasma concentrations of T_3 and TSH, were assessed at Baseline and each control time. Moreover, reverse T3 (rT3) was dosed before and after treatment in order to assess the putative pheriperal deiodination of l-LT4.

The mean plasma concentrations of rT_3T_3 and TSH and the changes from baseline at each control time were assessed by means of ANOVA for statistical significance.

9.6 DATA QUALITY ASSURANCE

To ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data, PharmaD&S SOPs were used as base for conduction of the study as applicable.

Training to the Principal Investigator and sub-investigators on study procedures had been performed during Site Initiation Visit. The investigators and the sub-investigators had ICH GCP training certificate available.

Study Investigator's manual was used by the staff during the study conduct as guide reference.

Five (5) monitoring visits were performed during the conduct of the trial. During these monitoring visits, all CRFs have been source verified 100% by PharmaD&S monitors.

Data base manual was used as base for the activity of the Data entry and data management. In order to permit data analysis, all data recorded in the study's CRF have been entered in the validated database. To ensure the correctness of entered data, a double data entry have been performed followed by a 100% quality control, executed by the administrator of the study.

Four (4) data queries emerged in the study during the review of the data entry. All of the data queries have been answered by the investigator and documented according PDS SOPS. The documentation has been archived in the study's TMF accordingly.

PharmaD&S Quality Assurance performed and audit review of the Clinical Study Report.

Laboratory Quality Assurance

The study has been performed in accordance with EMA/INS/GCP/532137/2010 guideline (Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples).

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Determination of Sample Size

Based on a prior experience conducted with a similar formulation (Certan et al. 2013) the mean value of T_4 was assumed to be 11.0 ± 1.2 pg/mL and a sample size of 26 subjects was estimated to allow confirming the stability of said value during the study within C.I. of ± 0.7 (99% C.I.). Assuming a dropout rate of 15% the decision was taken to enroll 30 subjects.

9.7.2 Statistical and Analytical Plans

The final analysis was performed after database lock on data transferred from SAS-PheedIt (eCRF) and after the finalization and approval of the SAP document. Three populations were defined for use in the descriptive and inferential statistical analyses: the Safety Population, the ITT Population, and the PP Population.

- "INTENTION TO TREAT" (ITT population): all subjects who received the study drug and who participated in at least one post-baseline assessment;
- "PER PROTOCOL" (PP Population): all subjects who concluded the study without important protocol deviations or violations;
- "SAFETY" (Safety Population): all subjects who will be received at least one dose of the study drug.

Screened subjects (n = 34)	→	Screening failures (n = 4)
↓		
Subjects who received at least one dose of the study drug (n= 30)	→	SAFETY POPULATION
↓		
Subjects who received the study drug and who participated in Control 1 (n = 30)	→	ITT POPULATION
↓	→	Drop-outs (n = 0) Major protocol deviations (n = 0)
Subjects who completed the study without major protocol deviations (n = 30)	→	PP POPULATION

All continuous variables were summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels were reported for all categorical measures. In general, all data were listed, sorted when appropriate by visit number, with the total population size relevant to that table, including any missing observations.

Variables from the CRF sections "Investigator confirmation of eligibility", "Screening failure" and "Treatment administration" were used to establish how many screened subjects reached the

treatment administration stage, how many screening failures and for what reasons (non-fulfilment of inclusion and/or exclusion criteria, AEs, withdrew consent or other).

Variables from the CRF section "Subject's completion of the study or premature discontinuation" were used to establish how many treated subjects completed the study, how many dropped out and for what reasons (protocol violation, adverse event, SAE, withdrew consent or other).

A skeleton diagram is provided in Annex IV listing the number of subjects screened, screening failure, treated, dropped out or completed.

9.7.3 Analysis on Demographic Characteristics

Only healthy Caucasian women aged between 18 and 50 years were enrolled in the study.

Quantitative data (age, height, weight, BMI) were summarized using quantitative descriptive statistics, such as mean, standard deviation, median, minimum and maximum values.

AEs, medical history and concomitant diseases were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 22.0.

All data were listed by subject and summarized by SOC and PT MedDRA® term.

Concomitant medications were not allowed at the Screening.

The complete list of concomitant medications was displayed by subject, indicating in addition to route, dose, indication, start and end date (or ongoing), even if due to AE, SAE or medical history.

No dietary changes of iodine-containing food or changes in the use of iodine-containing disinfectants, detergents or mouthwash products were allowed during the study. A maximum daily intake of iodized salt < 1,100 µg/day was allowed during the study. In order to check the compliance of the subjects with this requirement, the concentrations of iodide in the urine were assessed at the Screening and EOS.

9.7.4 Physical examination, vital signs and ECGs

Full physical examinations were performed at the Screening (Day -15 to Day 0), Baseline (Day 0), Day 42 (EOS). Information about the physical examination was recorded by the Investigator in the source documentation at the clinical site. Any abnormalities were recorded in the CRF. Significant findings/illnesses, reported after the start of the study and which met the definition of an AE, were recorded in the CRF.

Physical examination was presented by time point through descriptive statistics. Frequency of abnormalities was presented and compared by McNemar test, when applicable.

Subjects SBP/DBP (mmHg), HR (bpm), RF (bpm) and body temperature (°C) were measured by the Investigator or his/her deputy after 5 min of rest (sitting position). The measurements

were performed at:

- Screening (Day -15 to Day 0);
- Baseline (Day 1: pre-dose, and 5 hours post-dose);
- Day 1;
- Day 14;
- Day 28 (EOT);
- Day 42 (EOS).

Descriptive statistics and change *vs.* Baseline by time point were reported for each parameter. The values were compared *vs.* pre-treatment values using ANOVA.

A 12-leads ECG was performed at Screening and Day 42 (EOS).

ECG assessment was translated into: Normal, Abnormal but non clinically relevant (NCR), and Abnormal and clinically relevant (CR).

ECGs were summarized by presenting frequency tables of values falling outside normal ranges. Frequency of abnormalities was compared by McNemar test, when applicable.

9.7.5 Analysis of bioavailability

All variables were listed by subject.

All continuous variables were summarized by visit with n, mean, standard deviation, minimum and maximum and they were analyzed by ANOVA with visits.

All plasma concentrations encoded by Investigators (Normal, Abnormal NCR and Abnormal CR) were evaluated by frequency tables.

Plasma concentrations of T_4 ng/dL (continuous variable) were assayed at the following time points:

- Day 0 (pre-treatment), Day 0 (5 hours), Day 1 (24 hours), Day 14, Day 28 and Day 42.

The comparison of the means from baseline was performed with ANOVA.

Plasma concentrations of rT_3 (continuous variable) were assayed at the following time points:

- Day 0 (pre-treatment), Day 0 (5 hours), Day 1 (24 hours), Day 14, Day 28 and Day 42.

Plasma concentrations of T_3 µg/L (continuous variable) were assayed at the following time points:

- Day 0 (pre-treatment), Day 0 (5 hours), Day 1 (24 hours), Day 14, Day 28 and Day 42.

Plasma concentrations of TSH mUI/L (continuous variable) were assayed at the following time points:

- Day -15/0 (Screening), Day 0 (5 hours), Day 1 (24 hours), Day 14, Day 28 and Day 42.

The comparison of the means from baseline was performed with ANOVA.

9.7.6 Analysis on Safety and Local Tolerability

AEs/SAEs were recorded throughout the entire study duration.

The incidence of AEs/SAEs was evaluated by frequency tables providing, for each cross-classification and subcategory, the following frequencies:

- Total number of AEs/SAEs observed;
- Number and percentage of subjects reporting at least one AE/SAE.

When calculating the incidence of AEs, or any sub-classification thereof by time period, severity, etc., each subject was only counted once, and any repetitions of AEs were ignored; the denominator was the total population size.

Local tolerability of Somatoline® was assessed by the Investigator and the subjects throughout the collection of data in the subject diary during the entire study duration.

The Investigator assessed the local tolerability at the application site (both sides, left and right) on Day 0 after 5 hours after the first application, Day 1, Day 14, Day 28 and Day 42, by scoring (0-3) each of the following parameters (Table 4 - Section 14):

- Redness;
- Swelling;
- Hitching.

Frequency of scores was presented separately by itching, redness, and swelling, by treated thigh side and by day or by women.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Amendments

The protocol has not been amended during the study.

10 STUDY POPULATION

10.1 Disposition of Subjects

Based on a prior experience (Section 9.7.1), it was decided to enrol 30 subjects in order to have at least 26 subjects fully evaluated by assuming a dropout rate of 15%. To achieve the goal, the experimental site has screened 34 volunteers.

There were 4 volunteers who failed the screening, i.e. one volunteer who did fulfil the inclusion and exclusion criteria (Subject No. 4 because of ventricular extrasystoles) and three volunteers who withdrew their consent at the Day -15 Screening Visit (28-Feb-2019) before taking part in any study-related activity (Subjects No.8, 14, 15).

A total of 30 subjects were therefore enrolled in the study, and all of them (100%) completed the study.

No volunteer dropped out.

Subject accountability is summarized in Table 5 (Section 14) and in Table 14.1.1. The dates of each study visit per patient is presented in Listing L1 and in Table 14.1.2. The eligibility assessment by the investigators see Tables 14.3.X.X and Listings L12-L16. The completion rates of study are reported in Table 14.13.1.1 and Listings L33-L35.

10.2 PROTOCOL DEVIATIONS

There were no violation and no major protocol deviations (PDs).

Nineteen (19) subjects of the 30 enrolled have reported minor PDs, which consisted in:

- Day visit out of range;
- Incorrect laboratory procedure;
- Incorrect timing for returning the medication kit;
- No treatment for forgetfulness;
- SBP (94 mmHg) at screening out of range
- No urea analysis at the screening

All minor PDs were reported in Listing L2.

These minor PDs have not been considered to jeopardize the validity of the study results.

11 RESULTS

11.1 DATA SETS ANALYSED

All the 30 enrolled volunteers completed the study and were fully evaluated, with no major PDs. Thus, all the 30 volunteers were included in the Safety and Efficacy analysis without distinction between ITT and PP populations (Table 6 – Section 14).

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

11.2.1 Demographics

The demographic and baseline characteristics of the 30 enrolled volunteers are summarized in Table 7 (Section 14.1) and Tables 14.2.1.X and are listed by subject in Listing L3-L5x.

All the volunteers were Caucasians women according to the protocol.

The volunteers were aged between 18 to 47 years (mean ± s.d.: 33.3 ± 8.61 years), with a BMI ranging between 18.9 and 26.8 kg/m², as per the inclusion criteria (mean ± s.d.: 22.4 ± 2.2). The height ranged between 159 and 176 cm (mean ± s.d.: 165.1 ± 4.90 cm), and the weight ranged between 50 and 74 kg (mean ± s.d.: 61.2 ± 6.3 kg).

Lifestyle characteristics are summarized in Tables 14.2.3.X and listed in Listing L6, L7 and L8.

Pregnancy test results for female subjects are listed by subject in Listing L10 and Table 14.2.5.1 Virology in Listing L9. All pregnancy tests were negative, and all women used barrier contraceptive methods.

All drug screening tests were negative, and the use of alcohol and nicotine was within the inclusion criteria.

11.2.2 Concomitant Illnesses

No clinically relevant abnormalities were detected at the physical examination and laboratory analyses (see listing L24x and L25-L28). The ECG detected a case of ventricular extrasystoles in the Subject No 4, who was therefore excluded from the study (L23x).

11.2.3 Concomitant Medications

Seven (7) subjects took concomitant medications allowed by the protocol because of AEs. The concomitant medications – which were allowed by the protocol – are listed in Listings L11x and Tables 14.12.1.X.

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

All the thirty (30) subjects correctly completed the 28 days of treatment, excepted for:

- the Subject No. 2 and the Subject On. 24 who forgot to apply the Somatoline® gel for one (1) day;
- the Subject No. 27 who forgot to apply the Somatoline® gel for two (2) days (Tables 14.5.1.X).

Thus, in total four (4) days of non-treatment on 840 days of treatment (30 subjects x 28 days) were missed, equal to 0.5% that is 99.5% of compliance as reported by the subjects in their

diary.

11.4 SYSTEMIC BIOAVAILABILITY RESULTS AND TABULATIONS OF INDIVIDUAL SUBJECTS DATA

11.4.1 Plasma Concentrations

The plasma concentrations of T_4 (ng/dL) assayed at Day 0 (pre-treatment), Day 0 (5 hours), Day 1 (24 hours), Day 14, Day 28 and Day 42 are reported in Table 8 (Section 14.2), as well as in Tables 14.4.3.X and Listing 17. The trend over time of free T_4 is reported in Figure 1 (Section 14.2) (boxplot).

The average plasma concentration of T_4 was 1.13 ± 0.15 ng/dL at Baseline. After treatment with Somatoline® gel the free T_4 ranged between 1.09 ± 0.15 five hours after the first application (Control 1) to 1.14 ± 0.12 ng/dL 24 hours after the first application (Control 2), to 1.10 ± 0.12 at Control 3 (Day 14), to 1.11 ± 0.13 at EoT (Day 28), and to 1.13 ± 0.14 at EoS (Day 42).

As described by Table 8 and Figure 1 (Section 14.2), the mean T_4 values did not show any clinically relevant changes from Baseline, either during treatment or follow-up. The maximum average change from Baseline was a mean decrease of 0.04 ng/dL (-3.7%) at Control 1, but the one-way ANOVA for repeated measures did not demonstrate any statistically significant changes at any time.

The plasma concentrations of T_3 (ng/dL) assayed at Day 0 (pre-treatment), Day 0 (5 hours), Day 1 (24 hours), Day 14, Day 28 and Day 42 are reported in Table 9 (Section 14.2), as well as in Tables 14.4.5.X and Listing 17. The trend over time of T_3 is reported in Figure 2 (Section 14.2) (boxplot).

The average T_3 value was 3.83 ± 0.52 ng/dL at Baseline. After treatment with Somatoline® gel the T_3 values ranged between 3.52 ± 0.44 five hours after the first application (Control 1) to 3.83 ± 0.44 ng/dL 24 hours after the first application (Control 2), to 3.77 ± 0.42 at Control 3 (Day 14), to 3.80 ± 0.40 at EoT (Day 28), and to 3.67 ± 0.40 at EoS (Day 42).

The maximum average change from Baseline was a mean decrease of 0.31 ng/dL (-3.7%) at Control 1, which the one-way ANOVA for repeated measures has demonstrated to be statistically significant. The changes of the other control visits from pretreatment are not statistically significant.

The plasma concentrations of rT_3 (ng/dL) assayed at Day 0 (pre-treatment), Day 0 (5 hours), Day 1 (24 hours), Day 14, Day 28 and Day 42 are reported in Table 10 (Section 14.2), as well as in Tables 14.4.4.X and Listing 17. The trend over time of rT_3 is reported in Figure 3 (Section 14.2) (boxplot).

The average rT_3 value was 0.18 ± 0.04 ng/dL at Baseline. After treatment with Somatoline® gel the rT_3 values ranged between 0.20 ± 0.05 five hours after the first application (Control 1) to 0.18 ± 0.04 ng/dL 24 hours after the first application (Control 2), to 0.19 ± 0.06 at Control 3 (Day 14), to 0.20 ± 0.06 at EoT (Day 28), and to 0.20 ± 0.05 at EoS (Day 42).

The maximum average change from Baseline was a mean decrease of 0.02 ng/dL (-10%) at Control 1. The one-way ANOVA for repeated measures did not demonstrate any statistically significant changes at any time.

The plasma concentrations of TSH (mUI/L) assayed at Day 0 (pre-treatment), Day 0 (5 hours), Day 1 (24 hours), Day 14, Day 28 and Day 42 are reported in Table 11 (Section 14.2), as well as in Tables 14.4.2.X and Listing 17. The trend over time of TSH is reported in Figure 4 (Section 14.2) (boxplot).

The average TSH value was 1.90 ± 0.91 mUI/L at Baseline. After treatment with Somatoline® gel the TSH values ranged between 1.27 ± 0.48 five hours after the first application (Control 1) to 1.60 ± 0.82 mUI/L 24 hours after the first application (Control 2), to 1.61 ± 0.81 at Control 3 (Day 14), to 1.85 ± 1.00 at EoT (Day 28), and to 1.63 ± 0.75 at EoS (Day 42).

The maximum average change from Baseline was a mean decrease of 0.62 mUI/L (-26.5%) at Control 1, which the one-way ANOVA for repeated measures has demonstrated to be statistically significant. However, no other statistically significant difference was observed at the next visits.

11.4.2 Statistical / Analytical Issues

11.4.2.1 Adjustments for Covariates

Not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

All thirty (30) female subjects completed the study and no data were missing from the thyroid function assessment tests.

11.4.2.3 Interim Analyses and Data Monitoring

Not applicable.

11.4.2.4 Multicenter Studies

Not applicable.

11.4.2.5 Multiple Comparison / Multiplicity

Not applicable.

11.4.2.6 Use of an "Efficacy Subset" of subjects

Not applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.2.8 Examination of Subgroups

Not applicable.

11.4.3 Tabulation of Individual Response Data

In addition to Tables and Graphs representing group data reported in Section 14, individual data are reported in the Listing for Demographics (Listing L6, L7 and L8), Concomitant Medications (Listings L11x), Primary Efficacy Analyses (Listing 17), and Secondary Efficacy Analyses (Listing 17).

11.4.4 Drug Dose, Drug Concentration, and Relationship to Response

Not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable.

11.4.6 By-Patient Displays

Not applicable.

11.5 Systemic bioavailability Conclusions

After a 28-day cutaneous application of Somatoline® gel, the plasma concentrations of T_4 always remained within the normal range and they showed no clinically relevant changes across the different times from Baseline (1.13 ± 0.15 ng/dL) to EOT (1.11 ± 0.13 ng/dL), with a peak mean change from pretreatment values of 0.04 ng/dL (-3.7%) 5 hours the first application (not statistically significant). Likewise, the plasma concentrations rT_3 behaved in a similar way, with minor, not significant, changes 5 hours (Control 1) after Baseline.

The plasma concentration of T_3 and TSH were unchanged when the mean values at Baseline (3.83 ± 0.52 ng/dL and 1.54 ± 0.69 mUI/L, respectively) were compared to the values at the

EOT (3.80 ± 0.40 ng/dL and 1.85 ± 1.00 mUI/L, respectively). The ANOVA analysis showed two significant differences, which were considered not clinically relevant, i.e. a decrease of T_3 values to 3.52 ± 0.44 ng/dL at the Control 1 (Day 0 – 5 hours), and an increase of TSH to 1.90 ± 0.91 mUI/L at the Control 1 (Day 0 – 5 hours). No other statistically significant difference was observed at any time.

12 SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

All the 30 female subjects enrolled into the study correctly completed the required 28 days of treatment; in these subjects, the exposure to cutaneously applied Somatoline® gel was 20 grams/daily during the first 2 days, followed by 10 grams/daily for the next 26 days. The total exposure was therefore 300 grams of Somatoline® gel / 28 days, corresponding to T_4 3 grams / 28 days and escin 9 grams / 28 days.

Only 2 subjects (No. 2 and 24) have forgotten to apply the Somatoline® gel for only one day (1), and only one subject (N ° 27) has forgotten to apply the Somatoline® gel for two days. In total four (4) days of non-treatment on 840 days of treatment (30 subjects x 28 days), equal to 0.5% that is 99.5% of compliance as reported by the subjects in their diary.

12.2 ADVERSE EVENTS

12.2.1 Brief Summary of Adverse Events

Overall, eight (8) subjects (26.7%) reported at least one AE during the study. Eighteen (18) AEs were reported during treatment period and one (1) during follow up. AEs are summarized in Table 14.6.X.X.

No deaths or SAEs were reported.

12.2.2 Display of Adverse Events

A summary of AEs by SOC, PT and by relationship is presented in Table 12 (Section 14.3).

12.2.3 Analysis of Adverse Events

By PT, the AE headache was reported by the highest number of subjects during the study.

Five (5) subjects (16.7%) reported eight (9) AEs of headache. Four (4) cases in the subject No 29 (one during follow up) and two (2) in the subject No 16.

The subject No 31 experienced Erythema twice and the subject No 34 experienced Anxiety twice. All other AEs have been reported at most once.

RELATIONSHIP AND EXPECTEDNESS. Only the AEs of SOC "*Skin and subcutaneous tissue disorders*" were considered by the Investigator as related to the treatment with Somatoline®: "erythema" was considered as expected, while "pruritus" was considered as unexpected.

SEVERITY. All AEs were considered by the Investigator as not serious. No other severity rating was envisaged.

12.2.4 Listing of Adverse Events by Patient

All AEs are listed by subject in Listings L31-L33.

12.3 LOCAL TOLERABILITY

Local tolerability was reported daily by the subject in the diary and evaluated by the Investigator at any visit for symptoms of "redness", "swelling" and "itching", assigning scores from zero (0) to three (3) for both the right and left thighs (0: None, 1: Mild, 2: Moderate, 3: Severe).

Local tolerability results are listed by subject in Listings L29 and L30.

EVALUATION OF REDNESS.

Evaluation of redness is summarized in Tables 14.7.1.X. Three (3) subjects reported "1" score (Mild) for redness in their diary for a total of 9 days in both thighs; however, the Investigator has never detected any symptoms of redness at any visits.

EVALUATION OF SWELLING

Evaluation of redness is summarized in Tables 14.7.2.X. All thirty (30) subjects reported "0" score for swelling in all days of their diary; however, the Investigator has never detected any symptoms of swelling at any visits.

EVALUATION OF ITCHING

Evaluation of redness is summarized in Tables 14.7.3.X. Two (2) subjects reported "1" score (Mild) for itching in their diary for a total of 8 days in both thighs and 3 days in one thigh. The Investigator reported one (1) case of itching at EOT in both thighs, also reported among as AEs.

12.4 DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

No deaths or SAE were reported.

12.5 CLINICAL LABORATORY EVALUATION

12.5.1 Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal Laboratory Value (14.3.4)

Laboratory results are listed by subject in Listing L25 to L28.

EVALUATION OF LABORATORY RESULTS: HEMATOLOGY AND BLOOD CHEMISTRY

Laboratory results are summarized in Table 14.8.2.X. No clinically relevant abnormal results were reported; therefore, no statistical tests were performed.

EVALUATION OF URINALYSIS

Urinalysis assessments are summarized in Table 14.8.3.1. No clinically relevant abnormal results were reported; therefore, no statistical tests were performed.

EVALUATION OF IODURIA

Ioduria results are summarized in Table 14.8.4.X. No clinically relevant abnormal results were reported; therefore, no statistical tests were performed.

12.4 EVALUATION OF EACH LABORATORY PARAMETER

No additional evaluation of laboratory parameter has been performed.

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital signs results are shown in Table 13 (Section 14.3) and listed by subject in Listings L18-L22 and summarized in Table 14.9.X.X.

Five hours after the first application of Somatoline® there was an average decrease of 4.1 mmHg in SBP and of 5.1 mmHg in DBP after 48 days; however, these decreases in blood pressure were not statistically significant according to ANOVA with multiple comparisons of Tukey's method. There was an average decrease of 6.8 bpm in HR rate after 5 hours, but no statistically significant. No significant variation in respiratory rate and body temperature were observed.

The ECG results are listed by subject in Listing L23x and summarized in Table 14.10.1.1.

No clinically relevant abnormal results were reported, at the end of study, therefore no statistical tests were performed.

Physical examination findings are listed by subjects in Listing L24x and summarized in Table 14.11.1.1. All physical examination conditions were considered normal, except for a *Tinea versicolor* reported at the screening. Therefore, no statistical tests were performed.

12.6 SAFETY CONCLUSIONS

No deaths and no SAEs were reported overall the study period.

Eight (8) subjects (26.7%) reporting eighteen (18) AEs during treatment period and one (1) during follow up.

The AE "headache" was reported by the highest number of subjects (5 subjects [16.7%]). "Erythema" (expected) and "pruritus" (unexpected) were the only AEs considered related by the investigator.

As regards the local tolerability, the Investigator reported no signs of "redness" or "swelling", but one (1) case of "itching". Three (3) subjects (10%) reported mild redness and two (2) subjects (6.7%) reported mild itching in a few days of the 28 days of treatment.

There was no statistically significant variation from baseline in vital signs.

No clinically relevant abnormality over time were observed for the clinical laboratory results, 12-lead ECGs or physical examination findings.

13 DISCUSSION AND OVERALL CONCLUSIONS

The study has been aimed at investigating the bioavailability of l-T4 (primary objective) after a repeated cutaneous application of Somatoline® gel. Moreover the plasma levels of T_3, rT_3 and TSH were also evaluated with the objective to rule out a putative transcutaneous absorption of l-T_4, as active ingredient of Somatoline® gel, and its interference on systemic thyroid homeostasis. Finally, the local and systemic tolerability of Somatoline® gel were explored.

Blood levels of T_4 and T_3, rT_3 and TSH were measured during and after the Somatoline® gel administration. In compliance with the recommended dosage as per SmPC of Somatoline® emulsion, the study has been performed with a cutaneous application of Somatoline® gel for 28 consecutive days of treatment (20 grams/day on the first two days followed by 10 grams/day for the next 26 days), followed by a 14-day follow-up period.

30 Caucasian healthy women were enrolled in the study; the age ranged from 18 to 47 years and BMI from 18.9 to 26.8. Compliance to the treatment schedule was 99.5% and all PDs were considered minor. Blood samples for T_4, T_3 , $rT_3$and TSH levels were drawn at Baseline, 5

(Control 1) and 24 (Control 2) hours after the first application and thereafter on Days 14 (Control 3), 28 (EoT) and 42 (EoS).

The plasma concentrations of T_4 were not affected by the application of Somatoline® gel, at any time during the study.

Not clinically relevant changes were observed in the T_3 and TSH plasma concentrations, which showed a slight decrease of T3 and TSH five hours after the first Somatoline® gel application, albeit remaining in the normal ranges. These fluctuations could be explained by the different sample times (i.e. early in the afternoon at Control 1 *vs* early in the morning at basal, as per protocol) and the well established circadian rhythm of TSH and FT_3 [1-4]. No other changes were observed in the T_3 and TSH concentrations throughout the remaining part of the study,both at the medium (Control 2, EoT) and long (EoS) term.

No rT_3 change from basal has been observed throughout the study period, thus confirming no peripheral conversion of cutaneous locally applied l-T_4. Moreover, no change was observed at the medium (Control 2, EoT) and long (EoS) term of TSH, FT_3 and FT_4, suggesting a neutral/null effect of Somatoline® gel on systemic thyroid homeostasis.

The treatment resulted safe and well tolerated; no SAE occurred during the study. Two AEs (erythema and pruritus) were reported and considered possibly related to the treatment by the investigator.

14 TABLES, FIGURES AND GRAPHS

Table 1. Overall study schedule.

Timing of event		Screening	Baseline	Control 1	Control 2	Control 3	EOT	EOS
		Day -15 to Day 0	Day 0 (before dosing)	Day 0 +5 hours	Day 1 +24 hours	Day 14	Day 28	Day 42
Informed Consent		x						
Eligibility		x	x					
Demography & Lifestyle		x						
Medical History		x						
Haematology		x						x
Blood chemistry		x						x
Urine Drug Screening		x						
Urinalysis		x						x
Ioduria		x						x
Virology		x						
Alcohol/Nicotine Consumption		x						
TSH concentration[1]		x	x	x	x	x	x	x
Free T4, r-T3, T3[1]			x	x	x	x	x	x
Pregnancy Test		x	x					
Treatment[2]			x		x	x	x	x
Vital Sign (SBP, DBP, HR, RF, Temp)		x	x	x	x	x	x	x
Physical Examination		x	x					x
ECG		x						x
Adverse Events			x	x	x	x	x	x
Local Tolerability assessed	by investigators			x	x	x	x	x
	by subject (diary)			x	x	x	x	x

X[1]: T_4, rT_3, T_3 and TSH concentrations were evaluated at Baseline before dosing and 5 hours after dosing, at Day 1 (24 hours after dosing) , at Day 14, at Day 28 and Day 42

X[2]: the treatment was started after reconfirmation of eligibility criteria, a negative pregnancy test and plasma concentrations obtained. The treatment started on each thigh (10 grams) per day during the first two days, followed by 5 grams per thigh until the end of a 4-week period.

Table 2. Study Medication Characteristics

STUDY MEDICATION CHARACTERISTICS	
Generic/Trade Name:	Somatoline® gel
Chemical Name:	l-Thyroxine
Formulation:	Gel
Strength:	10%
Dose regimen:	10 grams gel (corresponding to l-T_4 10 mg and escin 30 mg) on each thigh per day during the first 2 days (20 grams per day in total), followed by 5 grams per thigh (10 grams per day in total) until the end of a 4-week period
Route of administration:	Topical (cutaneous)
Storage Conditions:	Room temperature and humidity

Table 3. Systemic bioavailability and Safety Measurements.

Timing of event		Screening	Baseline	Control 1	Control 2	Control 3	EOT	EOS
		Day -15 to Day 0	Day 0 (before dosing)	Day 0 +5 hours	Day 1 +24 hours	Day 14	Day 28	Day 42
Haematology		x						x
Blood chemistry		x						x
Urinalysis		x						x
Ioduria		x						x
TSH concentration[1]		x	x	x	x	x	x	x
Free T4, r-T3, T3[1]			x	x	x	x	x	x
Pregnancy Test		x	x					
Vital Sign (SBP, DBP, HR, RF, Temp)		x	x	x	x	x	x	x
Physical Examination		x	x					x
ECG		x						x
Adverse Events			x	x	x	x	x	x
Local Tolerability assessed	by investigators			x	x	x	x	x
	by subject (diary)			x	x	x	x	x

X[1]: T_4, rT_3, T_3 and TSH concentrations were evaluated at Baseline before dosing and 5 hours after dosing, at Day 1 (24 hours after dosing) , at Day 14, at Day 28 and Day 42

X[2]: the treatment was started after reconfirmation of eligibility criteria, a negative pregnancy test and plasma concentrations obtained. The treatment started on each thigh (10 grams) per day during the first two days, followed by 5 grams per thigh until the end of a 4-week period.

Table 4. Scores for the assessment of redness, swelling and hitching.

Score	0	1	2	3
Severity	None	Mild	Moderate	Severe

Table 5. Subject Accountability (All Subjects).

			Statistic	All
Screening	Day 15 to	Screened subjects	N	34
		Screening failures	N	4
		non-fulfilment of inclusion and/or exclusion	N	1
		withdrew consent	N	3
Baseline	Day 0	Enrolled subjects	N	30
Treatment	Day 1 to	Drop-outs	N (%)	0 (0.0%)
Follow-	Day 29 to			
EOS	Day 42	Subjects who completed the study	N (%)	30

N: number of subjects; n: number of subjects with data; %: percentages are based on the number of subjects randomized.

Source: Table 14.1.1 and Table 14.13.1.1

Table 6. Subject Accountability: Analysis Populations (all enrolled subjects).

	Statistic	All subjects
Number of subjects enrolled	N	30
Number of subjects in Safety Population	n (%)	30 (100.0%)
Number of subjects in ITT Population	n (%)	30 (100.0%)
Number of subjects in PP Population	n (%)	30 (100.0%)

N: number of subjects; n: number of subjects with data; %: percentages are based on the number of subjects randomized.

Source: Table 14.1.1 and Table 14.13.1.1

14.1 DEMOGRAPHIC DATA

Table 7. Demographics and Baseline Characteristics (All enrolled subjects)

Variable	Category	Statistic	All enrolled subjects
Gender	Female	n (%)	30 (100.0%)
Race	Caucasian	n (%)	30 (100.0%)
Age (years)		n	30
		Mean	33.3
		SD	8.61
		Minimum	18
		Median	32.5
		Maximum	47
Height (cm)		n	30
		Mean	165.1
		SD	4.9
		Minimum	159
		Median	164.0
		Maximum	176
Weight (kg)		n	30
		Mean	61.2
		SD	6.3
		Minimum	50
		Median	60.9
		Maximum	74
Body mass index (kg/m^2)		n	30
		Mean	22.4
		SD	2.2
		Minimum	18.9
		Median	22.6
		Maximum	26.8

N: number of all subjects; n: number of subjects with data; %: percentages are based on the number of subjects enrolled; SD: standard deviation.

Source: Tables 14.2.1.1 - 14.2.1.6

14.2 SYSTEMIC BIOAVAILABILITY DATA

Table 8. Plasma concentrations of T_4 (ng/dL)

VISIT	Mean Time	Free T4							
		N	Mean	Std	Min	Median	Max	95% LCL	95% UCL
Day 0 Baseline	08:30	30	1.13	0.15	0.82	1.17	1.44	1.08	1.19
Day 0 (5h) Control 1	13:47	30	1.09	0.15	0.82	1.12	1.46	1.03	1.14
Day 1 (24h) Control 2	08:49	30	1.14	0.12	0.90	1.15	1.51	1.10	1.19
Day 14 Control 3	08:54	30	1.10	0.12	0.86	1.10	1.39	1.06	1.15
Day 28 EoT	08:50	30	1.11	0.13	0.91	1.12	1.40	1.07	1.16
Day 42 EoS	08:57	30	1.13	0.14	0.87	1.12	1.52	1.08	1.18

Source: Tables 14.4.3.1

Figure 1. Trend over time of T_4 (Boxplot)

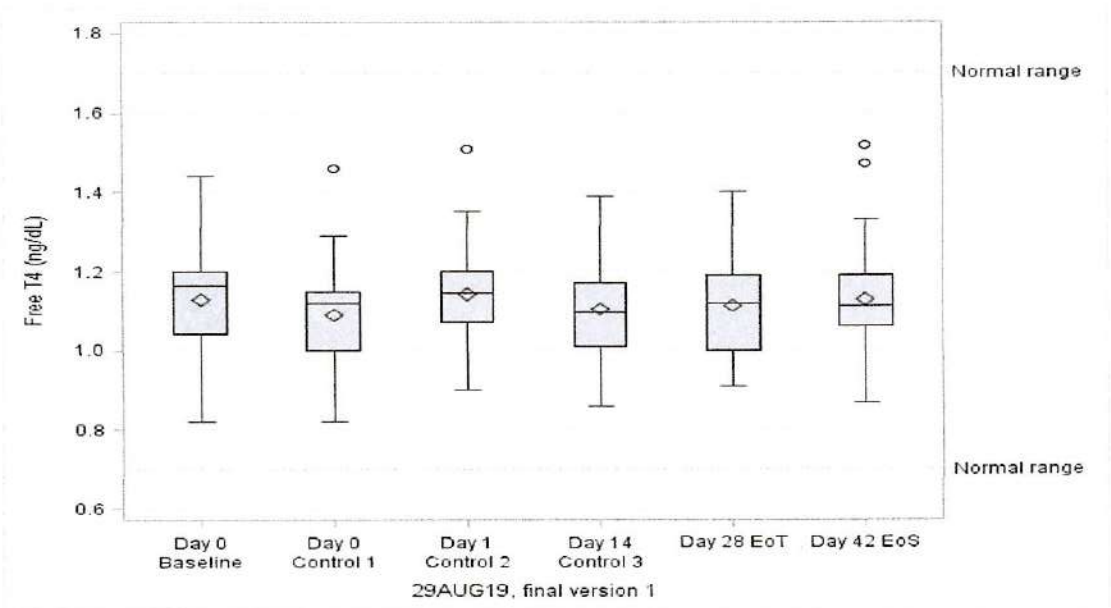


Table 9. Plasma concentrations of T_3 (ng/dL)

VISIT	Mean Time	T3							
		N	Mean	Std	Min	Median	Max	95% LCL	95% UCL
Day 0 Baseline	08:30	30	3.83	0.52	2.89	3.75	4.97	3.64	4.03
Day 0 (5h) Control 1	13:47	30	3.52	0.44	2.77	3.52	4.72	3.36	3.69
Day 1 (24h) Control 2	08:49	30	3.83	0.44	3.12	3.74	4.73	3.67	3.99
Day 14 Control 3	08:54	30	3.77	0.42	2.87	3.75	4.53	3.62	3.93
Day 28 EoT	08:50	30	3.80	0.40	3.06	3.74	4.57	3.65	3.95
Day 42 EoS	08:57	30	3.67	0.40	2.95	3.70	4.59	3.52	3.82

Source: Tables 14.4.5.1

Figure 2. Trend over time of T_3 (Boxplot)

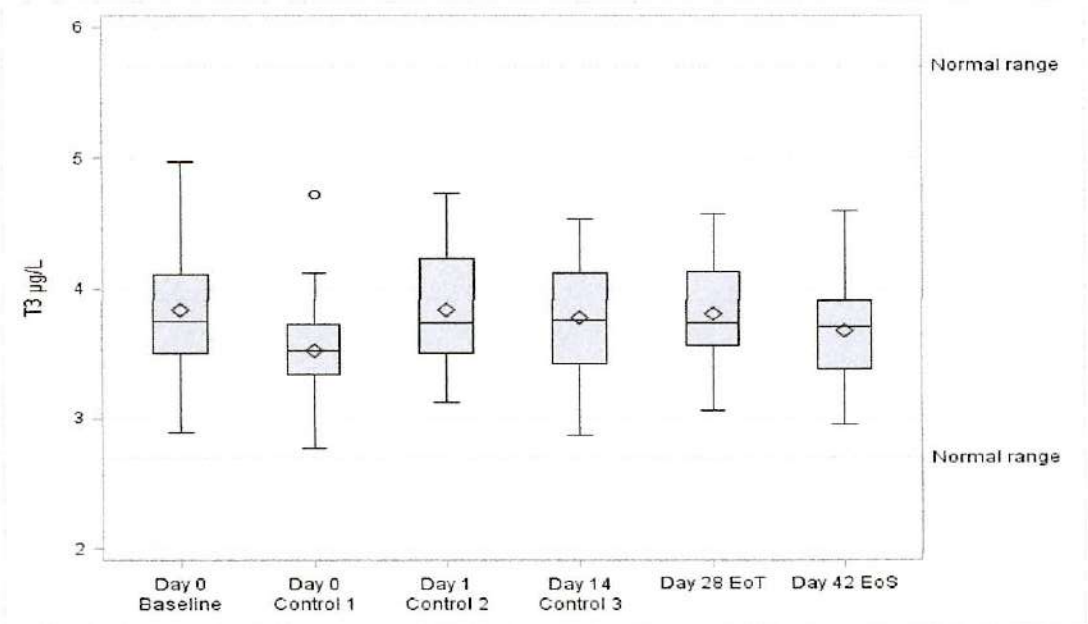


Table 10. Plasma concentrations of rT_3 (ng/dL).

VISIT	Mean Time	r T3							
		N	Mean	Std	Min	Median	Max	95% LCL	95% UCL
Day 0 Baseline	08:30	30	0.18	0.04	0.10	0.18	0.30	0.16	0.20
Day 0 (5h) Control 1	13:47	30	0.20	0.05	0.11	0.19	0.34	0.18	0.22
Day 1 (24h) Control 2	08:49	30	0.18	0.04	0.12	0.18	0.28	0.17	0.20
Day 14 Control 3	08:54	30	0.19	0.06	0.10	0.19	0.42	0.17	0.22
Day 28 EoT	08:50	30	0.20	0.06	0.10	0.19	0.33	0.18	0.22
Day 42 EoS	08:57	30	0.20	0.05	0.11	0.21	0.30	0.18	0.21

Source: Tables 14.4.4.1

Figure 3. Trend over time of rT_3 (Boxplot)

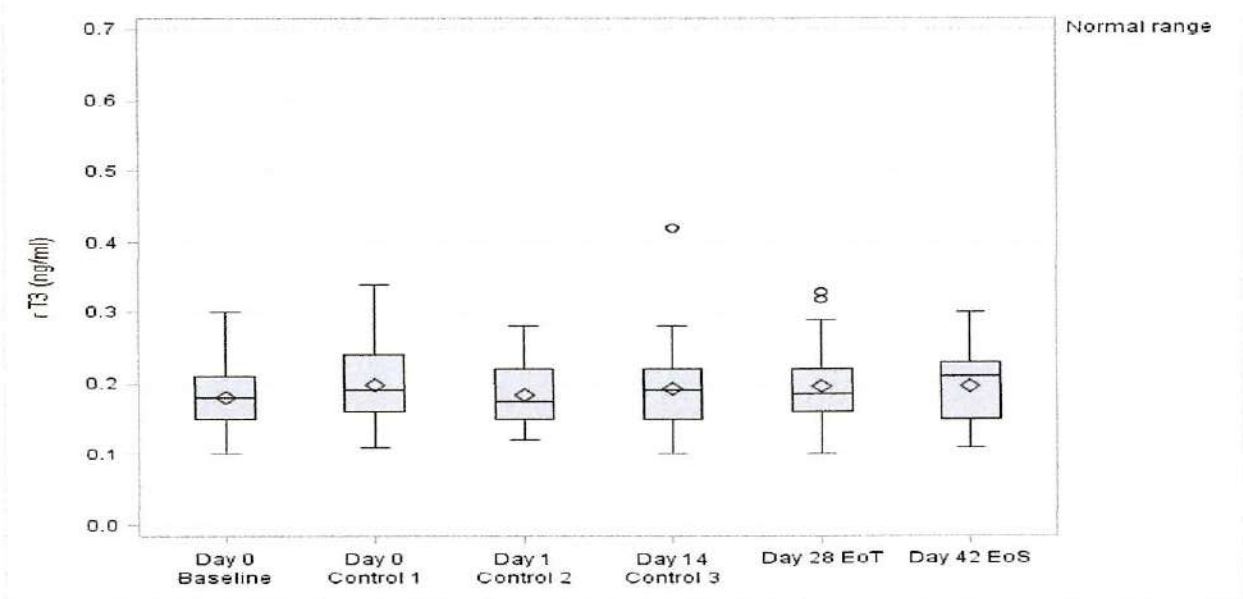
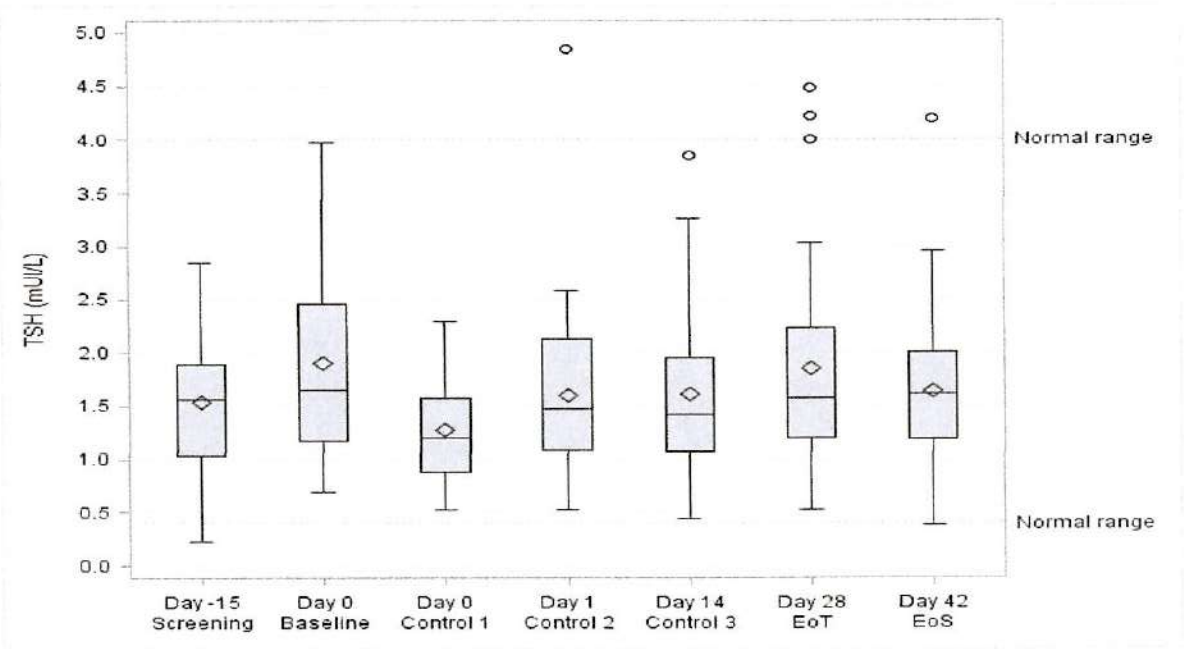


Table 11. Plasma concentrations of TSH (mUI/L)

VISIT	Mean Time	TSH							
		N	Mean	Std	Min	Median	Max	95% LCL	95% UCL
Day -15 Screening	09:47	30	1.54	0.69	0.23	1.56	2.85	1.29	1.80
Day 0 Baseline	08:30	30	1.90	0.91	0.69	1.65	3.98	1.56	2.24
Day 0 (5h) Control 1	13:47	30	1.27	0.48	0.53	1.47	2.29	1.10	1.45
Day 1 (24h) Control 2	08:49	30	1.60	0.82	0.53	1.47	4.85	1.29	1.90
Day 14 Control 3	08:54	30	1.61	0.81	0.44	1.42	3.85	1.31	1.92
Day 28 EoT	08:50	30	1.85	1.00	0.53	1.58	4.48	1.48	2.23
Day 42 EoS	08:57	30	1.63	0.75	0.38	1.62	4.20	1.35	1.91

Source: Tables 14.4.2.1

Figure 4. Trend over time of TSH (Boxplot)



14.3 SAFETY DATA

Table 12. Summary of All AEs by SOC, PT and relationship

System Organ Class Preferred Term	Number (%) of subjects		
	Not related N=30	Related N=29	Overall N=32
Gastrointestinal disorders			
Dyspepsia	1 (6.3%)		1 (5.3%)
Injury, poisoning and procedural complications			
Limb injury	1 (6.3%)		1 (5.3%)
Musculoskeletal and connective tissue disorders			
Back pain	1 (6.3%)		1 (5.3%)
Nervous system disorders			
Headache	9 (56.3%)		9 (47.4%)
Psychiatric disorders			
Anxiety	2 (12.5%)		2 (10.5%)
Insomnia	1 (6.3%)		1 (5.3%)
Reproductive system and breast disorders			
Premenstrual syndrome	1 (6.3%)		1 (5.3%)
Skin and subcutaneous tissue disorders			
Erythema		2 (66.7%)	2 (10.5%)
Pruritus		1 (33.3%)	1 (5.3%)
ALL	16 (100%)	3 (100%)	19 (100%)

Adverse events were coded using the Medical Dictionary for Regulatory Activities version 22.0.

Source: Table 14.6.2.2

Table 13. Change from baseline in vital signs.

	Baseline	Change from baseline				
	Day 0 N=30	5 h N=30	Day 1 N=30	Day 14 N=30	Day 28 N=30	Day 42 N=30
SBP (mmHg)	111.6 ±	-4.1 ± 7.5	-1.4 ± 8.6	-1.1 ± 9.0	-1.8 ± 7.9	0.1 ± 10.4
DBP (mmHg)	75.0 ± 7.5	-2.7 ± 7.4	-1.4 ± 7.3	-1.5 ± 6.9	-2.4 ± 6.5	-5.1 ± 5.9
HR (bpm)	75.5 ±	-6.8 ± 7.6	2.1 ± 9.1	-0.2 ±	-0.8 ±	-2.3 ± 10.6
RR (bpm)	15.9 ± 1.2	-0.1 ± 0.6	-0.2 ± 1.9	-0.2 ± 0.9	-0.2 ± 0.9	-0.4 ± 1.0
Body temper. (°C)	36.5 ± 0.4	0.1 ± 0.4	-0.0 ± 0.4	0.0 ± 0.5	0.0 ± 0.5	0.1 ± 0.4

15 REFERENCE LIST

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16 APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol

CLINICAL TRIAL PROTOCOL

INVESTIGATIONAL MEDICINAL PRODUCT (IMP):	Somatoline Gel
PROTOCOL N°:	Somagel
EUDRACT N°:	2018-002380-26
TITLE:	Single-group, open study on the systemic bioavailability, safety and local tolerability of a new gel formulation of Somatoline® in 30 healthy women.
SPONSOR:	Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni Via Baldanzese, 177, 50041 Calenzano – Firenze, Italy Tel: (+39) 055 8835320
SPONSOR STUDY MANAGER:	Cristina Sabatini e-mail address: csabatini@manettiroberts.it
CO-ORDINATING CENTER:	Clinical Pharmacology Centre for Drug Experimentation, University Hospital, Via Roma, 67, PISA, Italy
STUDY MONITORING:	CROnos Ricerche Cliniche srl via Tonale, 22 20125 Milano Italy tel. +39. 02. 67.38.28.69 fax. +39. 02. 67.38.28.68
DOCUMENT VERSION:	Final v1.0
DOCUMENT DATE:	09 July 2018
This study will be performed in compliance with Good Clinical Practices, including the archiving of essential documents.	
This protocol is confidential property of Manetti & Roberts, not to be copied or disclosed to third parties without written authorization from Manetti & Roberts.	

PROTOCOL ISSUING

SPONSOR STUDY MANAGER
Name, Surname: Cristina Sabatini
Address: Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni

Signature Cristina Sabatini *Date* 10 / 07 / 2018

R&D – PRODUCT INNOVATION MANAGER
Name, Surname: Barbara Tracuzzi
Address: Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni

Signature Barbara Tracuzzi *Date* 10 / 07 / 2018

STATISTICIAN
Name, Surname: Flavio Mascagni
Address: Pharmaceutical Development & Services S.r.l.

Signature _____ *Date* ____/____/____

PROTOCOL ISSUING

SPONSOR STUDY MANAGER
Name, Surname: Cristina Sabatini
Address: Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni

Signature _____ *Date* ____/____/_____

R&D – PRODUCT INNOVATION MANAGER
Name, Surname: Barbara Tracuzzi
Address: Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni

Signature _____ *Date* ____/____/_____

STATISTICIAN
Name, Surname: Flavio Mascagni
Address: Pharmaceutical Development & Services S.r.l.

Signature _____ *Date* 10/7/2018

PROTOCOL VERIFICATION

PRINCIPAL INVESTIGATOR
Name, Surname: Giovanni Gori
Address: Clinical Pharmacology Centre for Drug Experimentation, University Hospital

I have read this protocol and agree to conduct this trial in accordance with all the stipulations of the protocol and in accordance with the Declaration of Helsinki.

Signature _____ *Date* 11/JUL/2018

DOCUMENT HISTORY

Version Number	Date of issue	Short description of change/s and cross reference to eventual protocol amendment number
Final 1.0	09 July 2018	First Version

PROTOCOL SUMMARY

Title:	Single-group, open study on the systemic bioavailability, safety, local tolerability of a new gel formulation of Somatoline® in 30 healthy women.
Protocol N°:	Somagel
Eudract N°:	2018-002380-26
Study Site(s):	Clinical Pharmacology Centre for Drug Experimentation, University Hospital, Via Roma, 67, Pisa (Italy).
Study Objectives:	The primary objective of the study is to assess the systemic bioavailability of l-T_4 in female subjects with after repeated cutaneous of a gel formulation of Somatoline® according to the proposed posology as per Summary of Product Characteristics (SmPC) of emulsion Somatoline. The secondary objectives of the study are: • to assess the systemic bioavailability of rT_3, T_3 and TSH, after repeated cutaneous application of a gel formulation of Somatoline® in female subjects • to assess the local and systemic tolerability after repeated cutaneous application of a gel formulation of Somatoline® in female subjects
Study Population:	**Sample size:** based on a prior experience conducted with a similar formulation (Certan et al. 2013) mean value of FT4 was assumed to be 11.0 ± 1.2 pg/mL and a sample size of 26 subjects was estimated to allow confirming the stability of said value during the study within confidence interval of ±0.7 (99% confidence interval). Assuming a dropout rate of 15% the decision was taken to enroll 30 subjects. **Inclusion criteria:** healthy woman will be enrolled in the study if they meet all the following inclusion criteria: • *Sex and age*: Adult women aged between 18 and 50 years; • *Race*: Caucasian; • *Body mass index (BMI)*: 18.5 > BMI ≤ 30 kg/m^2; • *Vital signs*: systolic blood pressure (SBP) = 100-139 mmHg; diastolic blood pressure (DBP) = 50-89 mmHg; heart rate (HR) = 50-90 bpm, measured after 5 min of rest (sitting position); • *Electrocardiogram (ECG)*: no clinically relevant abnormalities at ECG (12 leads); • *Physical examination*: no clinically relevant abnormal physical findings; • *Laboratory analyses*: no clinically relevant abnormal laboratory values indicative of physical illness;

- *Allergy*: no ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients or ß lactam antibiotics;
- *Medical history*: no history of anaphylaxis to drugs or allergic reactions in general, no relevant history of renal, hepatic, cardiovascular, respiratory, skin, haematological, endocrine, or neurological diseases that may interfere with the aim of the study, no history of gastric mucosal damages, no neoplasia, no medications during 2 weeks before the start of the study, including OTC ("over the counter");
- *Participation in another experimental trial*: no participation in the evaluation of any experimental drug within 3 months prior to screening;
- *Blood donors*: no blood donations during 3 months prior to this study;
- *Drug or alcohol history*: no history of drug, alcohol (< 1 drink/day for females, defined according to USDA Dietary Guidelines 2000) or tobacco abuse (< 10 cigarettes/day);
- *Pregnancy*: not pregnant or lactating;
- *Contraception*: fertile women willing to use barrier contraceptive methods;
- *Subjects' capability*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study;
- *ICF*: signed written ICF prior to inclusion in the study;
- *Life-style:* Willingness of the subject to maintain a constant life style during the period of the study.

Exclusion criteria: Women will be excluded from the study if they meet anyone of the following inclusion criteria:

- *Pregnancy*: pregnant or lactating women;
- *ECG*: clinically relevant abnormalities;
- *Physical findings*: clinically relevant abnormal physical findings which could interfere with the study objectives;
- *Laboratory analyses*: clinically relevant abnormal laboratory values indicative of physical illness;
- *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considered to potentially affect the outcome of the study;
- *Diseases*: relevant history of renal, hepatic, gastrointestinal,

	cardiovascular, respiratory, skin, haematological, endocrine (in particular, thyroid), or neurological diseases, which may interfere with the aim of the study, history of gastric mucosal damages, neoplasia; • *Contraceptive*: changes (early or suspension) of the use of contraceptive oestrogen-progestin in the last 4 weeks, and inability to take adequate contraception during the study; • *Medications and diet*: any medication, including OTC, is forbidden during the screening period. Moreover: o In the 6 months before screening, any treatment with antithyroid drugs or any therapeutic use of iodine or iodine-containing medications (e.g., amiodarone, Somatoline®) is forbidden; o In the 6 months before screening, any diagnostic tests that led to the use of tracers, contrast agents containing iodine or iodine isotopes, is forbidden; o in the 4 weeks before screening, no changes in diet of foods containing iodine (e.g., iodized salt), or use disinfectants (e.g., betadine), detergents or any systemic or topical product containing iodine, including mouthwashes (e.g., Iodosan), toothpaste iodinated, douches, Lugol's solution; o In the 4 weeks before screening, any use of food supplements and herbal medicines; o a daily intake of iodized salt < 1,100 µg/day. • *Investigative drug trials*: participation in the evaluation of any experimental drug within 3 months prior to the start of the study; • *Blood donation*: blood donations during the 3 months prior to this study; • *Drug, alcohol, tobacco*: history of drug, alcohol [> 1 drink/day for females defined according to USDA Dietary Guidelines 2000] or tobacco abuse (> 10 cigarettes/day).
Study Design:	The study will be run according to a single-group, open design.
Treatment:	Somatoline® 10 g gel (l-T_4 10 mg/escin 30 mg) will be applied daily 10 grams on each thigh (20 grams per day in total) during the first 2 days, *followed by 5 grams per thigh (10 grams per day in total) until the end of* a 4-week period, starting from the day the first dose was applied. The subjects have to apply the product and then massage the skin of the entire thigh for several minutes until completely absorbed.
Evaluation parameters:	**Primary end-point** - Blood samples for measurement of TSH concentrations will be collected during the Screening (Day -15 to Day 0), Control 1 (Day 0 – Hour 5), Control 2 (Day 1), Control 3 (Day 14) and End of Treatment (Day 28). The assessments will be repeated at End of

	Study (Day 42) after a 14-day follow-up, during which no treatment will be performed. Apart from the Control I assessment, all blood samples will be collected at the same time of the day, with a time window of ± 1 hour. **Safety assessment** - Safety of the tested formulation will be evaluated based on the record of any AE and SAE. Moreover, the local tolerability at the application site will be assessed by both the investigator (medical visit) and the subject (diary), throughout the entire study duration.
Statistical analysis:	To assess the systemic bioavailability of l-T4 (primary endpoint) and rT3, T3, TSH, (secondary endpoints) after repeated cutaneous application of a gel formulation of Somatoline® in female subjects, ANOVA will be used. Frequency tables will be provided for adverse events and local tolerability, as well as for abnormalities detected with ECG, laboratory data and vital signs.
Expected starting date:	Date 30 October 2018
Expected ending date:	Date 28 February 2019

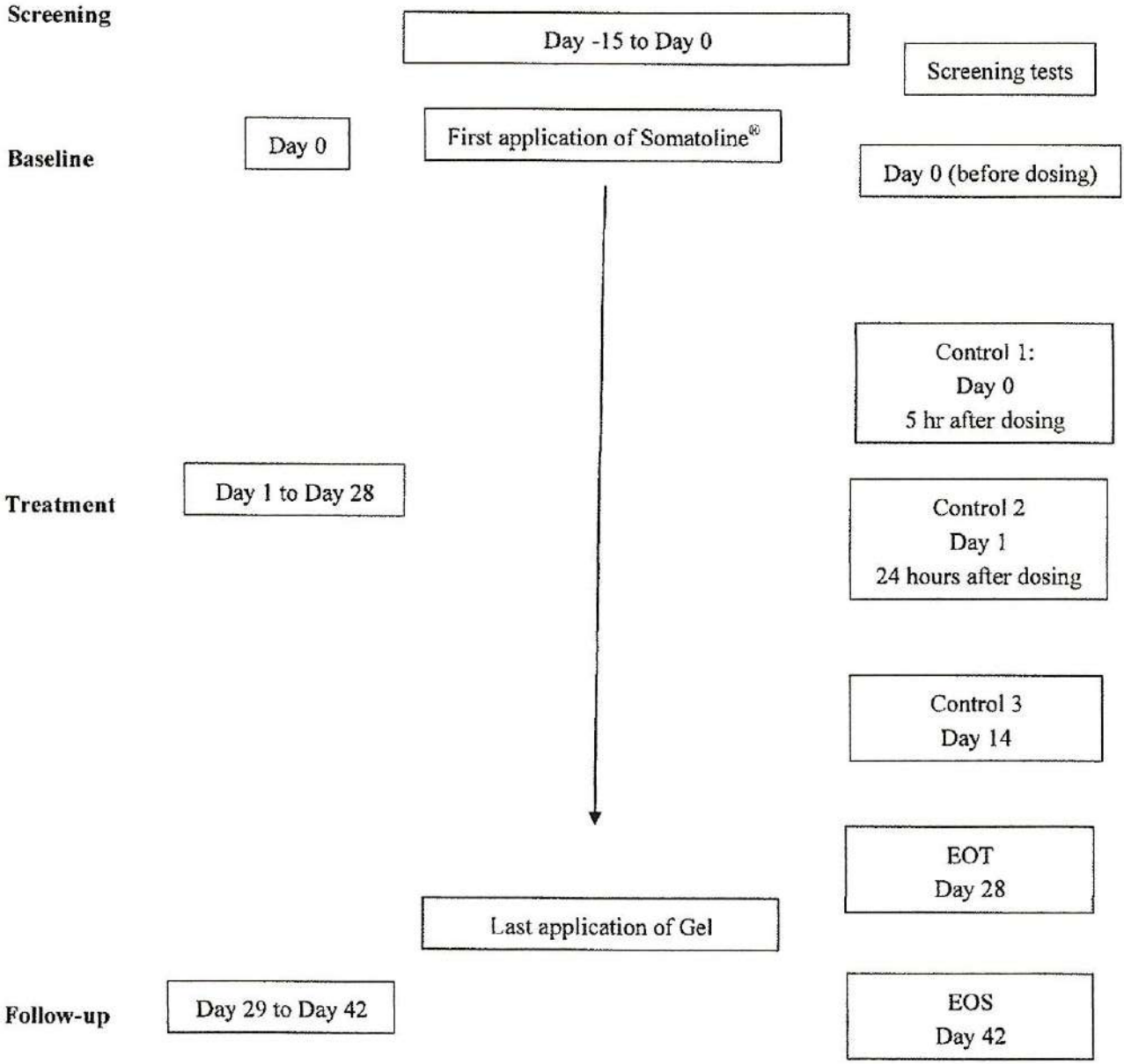
OVERALL STUDY SCHEDULE

Timing of event	Screening	Baseline (before dosing)	Control 1 Day 0	Control 2 Day 1	Control 3 Day 14	End of Treatment	End of Study (Follow-up)
	Day -15 to Day 0	Day 0	5 hours	24 hours	Day 14 +1	Day 28 +3	Day 42
Informed Consent	x						
Eligibility	x	x					
Demography & Lifestyle	x						
Medical History	x						
Hematology	x						x
Blood chemistry	x						x
Urine Drug Screening	x						
Urinalysis	x						x
Ioduria	x						x
Virology	x						
Alcohol/Nicotine Consumption	x						
TSH concentration[1]	x	x	x	x	x	x	x
Free T4, r-T3, T3[1]		x	x	x	x	x	x
Pregnancy Test	x	x					
Treatment[2]		x		x	x	x	x
Vital Sign (SBP, DBP, HR, RF, Temp)	x	x	x	x	x	x	x
Physical Examination	x	x					x
ECG	x						x
Adverse Events		x	x	x	x	x	x
Local Tolerability assessed by investigators			x	x	x	x	x
Local Tolerability assessed by subject (subject diary)			x	x	x	x	x

X[1]: Free T4, r-T3, T3 and TSH concentrations will be evaluated at Baseline before dosing and 5 hours after dosing, at Day 1 (24 hours after dosing) , at Day 14, at Day 28 and Day 42

X[2]: the treatment will start after the eligibility criteria reconfirmed, a negative pregnancy test and plasma concentrations obtained. The treatment starts on each thigh (10 grams) per day during the first two days, followed by 5 grams per thigh until the end of a 4-week period.

STUDY FLOW CHART



LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BMI	Body Mass Index
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Coefficient Of Variability
DBP	Diastolic Blood Pressure
ECH	Electrocardiogram
EOS	End-Of-Study
EOT	End-Of-Treatment
FT4	Free Thyroxine
GLP	Good Laboratory Practices
HB	Hepatitis B
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference Of Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
MCH	Mean Concentration Of Haemoglobin
MCV	Mean Corpuscular Volume
M&R	Manetti & Roberts
NCA	National Competent Authority
OTC	Over The Counter
PI	Principal Investigator
PP	Per Protocol
RBC	Red Blood Cells
R&D	Research and Development
RF	Respiratory Frequency
rT3	Reverse Triiodothyronine
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SF	Screening Failure
SUSAR	Suspected, Unexpected Serious Adverse Drug Reaction
T3	Triiodothyronine
TOST	Two-One-Sided T-Test

TSH..... Thyroid Stimulating Hormone
USDA ..... United States Dietary Allowance
WBC ..... White Blood Cells

TABLE OF CONTENTS

PROTOCOL SUMMARY		5
OVERALL STUDY SCHEDULE		9
STUDY FLOW CHART		10
TABLE OF CONTENTS		13
1	**ORGANISATIONAL AND ADMINISTRATIVE ASPECTS**	16
1.1	STUDY SITE	16
1.2	LABORATORY	16
1.3	CONTRACT RESEARCH ORGANIZATION (CRO) AND STUDY MONITORING	16
1.4	DATA MANAGEMENT & STATISTICAL ANALYSIS	16
1.5	DRUG SAFETY	16
1.6	CLINICAL QUALITY ASSURANCE	16
2	**INTRODUCTION**	17
2.1	BACKGROUND INFORMATION	17
2.2	RATIONALE	18
2.3	POTENTIAL RISKS AND BENEFITS	19
3	**TRIAL OBJECTIVES**	19
3.1	PRIMARY OBJECTIVE (S)	19
3.2	SECONDARY OBJECTIVE(S)	19
3.3	END POINT(S)	19
4	**TRIAL DESIGN**	19
5	**SELECTION OF POPULATION**	20
5.1	SUBJECTS SELECTION	20
5.2	INCLUSION CRITERIA	20
5.3	EXCLUSION CRITERIA	21
5.4	WITHDRAWAL OF SUBJECTS	22
5.5	PREMATURE TERMINATION	22
6	**TREATMENTS**	23
6.1	INVESTIGATIONAL MEDICINAL PRODUCT	23
6.2	DOSAGE AND ADMINISTRATION	23
6.3	PACKAGING AND LABELLING	23
6.4	STORAGE AND ACCOUNTABILITY	23
6.5	CONCOMITANT MEDICATIONS AND STUDY RESTRICTIONS	24
6.6	PRECAUTIONS/OVERDOSAGE	24
6.7	TREATMENT ALLOCATION AND RANDOMISATION PROCEDURES	24
6.8	EMERGENCY CODE AND UNBLINDING PROCEDURES	24
7	**STUDY PROCEDURES**	24

7.1	OVERALL STUDY SCHEDULE	24
7.2	SCREENING (DAY -15 TO DAY 0)	24
7.3	BASELINE (DAY 0)	24
7.4	CONTROL 1 (DAY 0 – 5 HOURS AFTER THE FIRST APPLICATION)	25
7.5	CONTROL 2 (DAY 1 - 24 HOURS)	25
7.6	CONTROL 3 (DAY 14)	25
7.7	END OF TREATMENT (DAY 28)	25
7.8	END OF STUDY (DAY 42)	25
8	**OTHER STUDY MATERIAL**	26
9	**MEASUREMENT OF EFFICACY AND SAFETY VARIABLES**	26
9.1	PRIMARY EFFICACY VARIABLES	26
9.2	SAFETY VARIABLES	26
9.2.1	*Physical examination*	26
9.2.2	*Vital signs*	27
9.2.3	*ECGs*	27
9.2.4	*Clinical laboratory assays*	27
9.2.5	*Local tolerability assessment, throughout the entire study duration*	28
10	**ADVERSE EVENTS DESCRIPTION & REPORTING**	28
10.1	DEFINITION OF ADVERSE EVENT	28
10.2	TIME PERIOD, FREQUENCY, AND METHOD OF DETECTING AES AND SAES	30
10.3	RECORDING OF AES AND SAES	30
10.4	ASSESSMENT OF AE RELATIONSHIP TO TREATMENT.	30
10.5	EXPEDITED REPORTING OF SAES	31
10.6	FOLLOW-UP OF SAE/SADRS	31
10.7	REPORTING OF SUBJECT DEATH	31
10.8	REPORTING OF PREGNANCIES	31
10.9	SAFETY OBLIGATIONS OF THE SPONSOR	31
11	**DATA MANAGEMENT AND STATISTICAL ANALYSIS**	32
11.1	DATA MANAGEMENT AND DATA QUALITY ASSURANCE	32
11.1.1	*Data collection / CRF*	32
11.1.2	*Coding Dictionaries*	32
11.2	STATISTICAL ANALYSIS	32
11.2.1	*Statistical hypotheses*	32
11.2.2	*Sample size*	33
11.2.3	*Population for analysis*	33
11.2.4	*Missing data*	33
11.2.5	*Protocol deviations*	33
11.2.6	*Interim analysis*	33
11.2.7	*Statistical methods*	33

11.3	BIOLOGICAL SAMPLES	34
12	**MONITORING AND ACCESS TO DATA**	34
12.1	MONITORING	34
12.2	QUALITY CONTROL AND QUALITY ASSURANCE	34
13	**ETHICAL AND REGULATORY ASPECTS**	35
13.1	DECLARATION OF HELSINKI	35
13.2	NCA AND IEC APPROVAL	35
13.3	PROTOCOL AMENDMENTS	35
13.4	WRITTEN INFORMED CONSENT	36
13.5	INSURANCE	36
13.6	CONFIDENTIALITY	36
14	**LOCATION OF DATA**	37
15	**REPORTING**	37
16	**PUBLICATION POLICY**	37
17	**RESPONSIBILITIES**	38
17.1	SPONSOR	38
17.2	CLINICAL CENTER	38
17.3	CRO	38
18	**REFERENCES**	38
19	**APPENDICES**	38
19.1	APPENDIX I : SAMPLE OF STUDY MEDICATION LABELS	39
19.1.1	PRIMARY PACKAGING	39
19.1.2	SECONDARY PACKAGING	40
19.2	APPENDIX II: SAMPLE OF SUBJECT CARD	41

1 ORGANISATIONAL AND ADMINISTRATIVE ASPECTS

1.1 STUDY SITE

The study will be run at the Clinical Pharmacology Centre for Drug Experimentation, University Hospital, via Roma 67, I-56126 Pisa (Italy).

Principal Investigator (PI): Dr Giovanni Gori
E-mail: giovannigori.gori@gmail.com
Phone: +39-050-993240; Fax: +39-050-993240;

1.2 LABORATORY

Laboratory analyses will be performed at the study clinical site. Analytical facilities and procedures are in compliance with GLPs regulations.

1.3 CONTRACT RESEARCH ORGANIZATION (CRO) AND STUDY MONITORING

CROnos Ricerche Cliniche srl. via Tonale, 22, 20125 Milano Italy

Project Manager: Dr. Elisabetta Di Martino
Email: edimartino@cronos.srl
Mobile: +39-345-9966300

1.4 DATA MANAGEMENT & STATISTICAL ANALYSIS

Statistician: *Dr. Flavio Mascagni*
Email: mascagniflavio@gmail.com
Phone: +39-0575 66999;

1.5 DRUG SAFETY

All serious adverse events (SAE), whether or not deemed drug-related or expected, must be reported in writing by using the SAE Form by the PI within 24 hours (one working day) of first becoming aware of the event to:

Email: farmacovigilanza@pharmades.it; Tel: +39-055-7224179; Fax: +39-055-7227014.

The report is made by the Investigator in writing by email and/or by fax, by meaning the form designated for serious adverse event reporting (SAE Report Form).

1.6 CLINICAL QUALITY ASSURANCE

The study will be conducted and monitored by Pharma D&S under the sponsorship of M&R Spa.
The clinical trial will be conducted according to ICH-GCP E6R2. The CRO will be responsible for data processing (that includes also data validation, errors resolution, quality control verification of efficacy/safety defined variables) according to the procedures established with the sponsor. The database will be closed after that all data will be considered complete and accurate by the coordination of the trial.
The sponsor, or the sponsor's representative, may conduct audits at the investigational sites. The PI agrees to participate with audits conducted at a reasonable time, in a reasonable manner.

2 INTRODUCTION

2.1 BACKGROUND INFORMATION

The "edematous fibrosclerotic panniculopathy" - more commonly known as "cellulite" - is a localized metabolic disorder of the subcutaneous layer of skin, the dermis, and its small blood vessels. Over years, these vessels become compressed, resulting in inflammation, poor lymph drainage, proliferation of fibrous tissue, tissue damage, unevenness of the thickness of the skin, and the protrusion (herniation) of fat through layers of the skin. The primary areas involved - the thighs, abdomen, and buttocks - acquire the uneven, dimpled, and textured skin of an orange (peau d'orange) or the lumpiness of cottage cheese. Cellulite is common and found in from 85 to 98% of post-adolescent females (though more often in Caucasian than Asian or Black women). It is rarely seen in males but is more common in males with androgen-deficient states, such as Klinefelter's syndrome, hypogonadism, post-castration states and in those subjects receiving oestrogen therapy for prostate cancer.

The causes of cellulite include changes in metabolism, physiology, dieting too hard or too much, sex-specific dimorphic skin architecture, alteration of connective tissue structure, hormonal factors, genetic factors, microcirculatory system, extracellular matrix, and subtle inflammatory alterations (Avram 2004; Pavicic et al. 2006). As mentioned above, cellulite is not a static condition. If left untreated, it can get worse. Early intervention may help reduce or even prevent its insidious progression. Indeed the following stages occur during cellulite formation (Marenus, 1997):

- STAGE ONE: it involves a deterioration of the skin dermis, whereby the integrity of the blood vessels and capillaries that create a complex transport network throughout the skin slowly begins to break down. Similarly, the upper region of the dermis begins to lose some of its capillary network. Fat cells, housed within the freestanding fat cell chambers, begin to engorge with lipids, often swelling 2-3 times their original size. Fat cell clumping may commence at this stage as well. Fluid begins to accumulate in the tissue, most likely due to a breakdown in the capillary system. Projections of fat begin to occur in the dermis and there is an increase in glycosaminoglycans, which may account for the enhanced ability for tissues to retain excess water.
- STAGE TWO: dermal deterioration increases, and the microcirculatory system continues to decline. Fat cells engorge further, and clumping is more pronounced, so that the compression of the blood vessels keeps on increasing. The appearance of gaps in the dermis, which may be the result of the normal inflammatory process, is common. Such process activates specific enzymes such as collagenase and elastase, creating an available path for immune cells to migrate to the site of inflammation. Fluids continue to accumulate. At this stage, "orange peel" skin is evident.
- STAGE THREE: the microcirculatory system continues to deteriorate, slowing metabolism in the cells of the dermis. Both protein synthesis and the repair process are reduced drastically, which may contribute to a thinning of the dermal layer. Protein deposits begin to form around fat cell clusters. Pinching the skin between finger and thumb at this stage demonstrates a definite "orange peel" effect.
- BY STAGE FOUR, hard nodules are evident in the dermal region. These are comprised of fat cell clumps encased in a hardened protein shell.

Somatoline® is a medicinal product that has been authorized for marketing in Italy since November 1973 for the treatment of localized adiposity accompanied by cellulite. The product is today manufactured as cutaneous emulsion containing l-thyroxine (l-T_4) at the concentration of 0.1% (i.e., 100 mg per 100 gr of emulsion) and escin at the concentration of 0.3% (i.e., 300 mg per 100 grams of emulsion); the product is sold as 10-g sachets for cutaneous application.

The active ingredients of Somatoline® exert their activity mainly on adipose tissue, activating the process of hydrolysis and mobilization of triglycerides and fatty acids, and developing an inhibitory action on the synthesis of lipids. They act also on the permeability of the capillaries, exerting anti-oedema action and removal of stagnant liquids in the tissues, playing a mobilizing effect at the tissue level of saline water collected, frequently found in the tissues affected by cellulite.

Somatoline® has been reported to show a consistent tolerability across the years.

Since 1995 up to December 2016, it has been estimated that 8.359.197 packs of Somatoline® have been sold, which are equivalent to 208.757.975 doses (1 dose corresponding to 1 sachet or to 2 sprays) covering about 5.218.949 cycles of treatment (40 consecutive days, using 1 dose of 10 g per day). Thus, assuming that to each cycle corresponds a subject, it is estimated that a total number of about 5.218.949 have been exposed to Somatoline®. During this long period, the evaluation of the cumulative safety data and the benefit-risk analysis have confirmed the favourable safety profile of the medicinal products (PSUR, 2017).

The safety of use is supported by bioavailability studies performed after cutaneous administration, which document the absence of any significant systemic absorption of the active compound. In particular, Buraglio (1997) demonstrated that topical application of l-T4, did not affect physiological levels of pituitary - thyroid hormones, finding which was further clinically confirmed by Galbiati et al. (2002) and more recently by in vitro studies performed by Padula et al. (2008).

More recently, Certan et al. (2013) have assessed the systemic effects of a cycle of treatment with the emulsion formulation of Somatoline® (l-T_4 and escin in healthy women based on changes in bioavailability of free l-T_4, free l-T_3, reverse l-T_3 (rT_3), and thyroid stimulating hormone (TSH). The study enrolled 20 healthy adult women with a body mass index (BMI) lower than 30, not exposed to iodine-containing products. The study called for 28 consecutive days of treatment with Somatoline® followed by a 14-day follow-up period. Blood samples for free T_4, free T_3 and TSH levels were drawn at baseline, 5 and 24 hours after the first application and thereafter on days 14, 28 and 42. Levels of rT3 were measured during the first 24 hours post-application.

Subject mean age was 40.1 ± 8.0 years and BMI from 19.1 to 29.8. Levels of free T_4 always remained within normal range and did not change in a clinically relevant way from baseline (11 ± 1.2 pg/dL), with maximum mean change from pre-treatment values of 0.4 pg/mL ($p = 0.87$). Likewise, free T_3 and TSH levels did not change significantly from baseline (3 ± 0.4 pg/dL and 1.8 ± 0.9 μU/mL, respectively). Levels of rT_3 behaved in a similar way, with modest changes from baseline ($p = 0.29$). Local tolerability was defined "excellent" for 19 out of 20 women (95%) and "moderate" in one subject who experienced the onset of folliculitis, for which causal correlation with the treatment was considered "possible".

Thus, once Somatoline® is used under the recommended modes of use, the application of the product does not affect plasma levels of T_4, T_3, rT_3 and TSH, either in the short term or after 28 days (Certan et al. 2013).

2.2 RATIONALE

Somatoline® has been actually developed in the pharmaceutical form of gel. The quali- and quantitative composition of Somatoline® gel is reported in the following:

Somatoline® gel Ingredients

Cod. MP	MATERIE PRIME	%
R162008	Acqua demi.	89,42
R104812	L-Tiroxina micronizzata	0,10
R096181	Escina	0,30
R094693	Gomma Xantana	0,20
-	Carbopol 980 (Lubrizol)	0,40
-	Trietanolammina (Carlo Erba)	0,38
R010261	Sorbitolo sol. 70%	3,00
R053451	Imidazolidinyl urea	0,30
-	Alcol Etilico 96 (Distilleria Scardina)	5,00
R170821	Profumo Rose 10138D	0,10
-	Fenossietanolo (Faravelli)	0,80
		100

SOMATOLINE GEL	
acqua	89,40g
alcol etilico 96%	5,00g
sorbitolo	3,00g
fenossietanolo	0,80g
carbopol 980 NF	0,40g
trietanolammina	0,38g
imidazolidinyl urea	0,30g
escina	0,30g
gomma xantan	0,20g
levotiroxina	0,10g
profumo	0,10g
TOT	100,00 g

2.3 POTENTIAL RISKS AND BENEFITS

The general and local safety of use of Somatoline® is documented by biochemical and pharmacological evidences, as well as by the previously performed studies of bioavailability, which have documented that no clinically relevant amounts of T_4 are systemically absorbed after repeated cutaneous application of the marketed Somatoline® emulsion (Somatoline® Investigator's Brochure v. 2 of 3rd July 2018). No absorption of significant amounts of T_4 are also expected with Somatoline® gel and, therefore, the risks for subjects who accept to participate in this study are expected to be identical to those related to current use of Somatoline® emulsion in the standard daily body care.

3 TRIAL OBJECTIVES

3.1 PRIMARY OBJECTIVE (S)

The primary objective of the study is to assess the systemic bioavailability of l-T_4 in female subjects with local cellulitis after repeated cutaneous of a gel formulation of Somatoline® according to the proposed posology as per Investigator's Brochure.

3.2 SECONDARY OBJECTIVE(S)

The secondary objectives of the study are:

- to assess the systemic bioavailability of T_4, rT_3, and TSH, after repeated cutaneous application of a gel formulation of Somatoline® in female subjects with local cellulitis;
- to assess the local and systemic tolerability after repeated cutaneous application of a gel formulation of Somatoline® in female subjects with local cellulitis.

3.3 END POINT(S)

The primary end-point is the comparison of the pre-treatment plasma concentrations of l-T_4 with those observed 24 hours, 14 days and 28 days after a cutaneous repeated application of Somatoline® gel, and 14 days after the last application of the gel (Day 42 of follow-up).

The secondary end-point is the comparison of the plasma concentrations of T_3, rT_3, and TSH with those observed 24 hours, 14 days and 28 days after a cutaneous repeated application of Somatoline® gel, and 14 days after the last application of the gel (Day 42 of follow-up).

4 TRIAL DESIGN

The study will be run according to a single-group, open design.

Briefly, a group of 30 Caucasian healthy woman, aged between 18 and 50 years, will be selected for the participation into the study, during a Screening period which cannot last more than 15 days (Day -15 to Day 0).

Women will be early informed about the purposes of the study and the risks related to the study participation. If they agree to participate, they will be consented with the most recently approved Informed Consent Form (ICF), and then evaluated for their compliance to the inclusion and exclusion criteria. Once the eligibility of women has been confirmed, they will be assessed for plasma concentrations of T_4, T_3, rT_3 and TSH.

No dietary changes of iodine-containing food or changes in the use of iodine-containing disinfectants, detergents or mouthwash products will be allowed during the study. A maximal daily intake of iodized salt of 1,100 µg/day is allowed. In order to check the compliance of the subjects with this requirement, the concentrations of iodide in the urine will be assessed at the Screening and End of Study (EOS).

At Baseline (Day 0), after a medical visit has reconfirmed the eligibility criteria and a negative pregnancy test has been obtained, the women will be assessed again for plasma concentrations of T_4, T_3, rT_3 and TSH.

After these examinations, women will be instructed to apply Somatoline® 10 g gel (l-T_4 10 mg/escin 30 mg) on each thigh per day during the first 2 days (20 grams per day in total), followed by 5 grams per thigh (10 grams per day in total) until the end of a 4-week period starting from the day the first dose was applied. The subjects have to apply the product and then massage the skin of the entire thigh for several minutes until completely absorbed.

Blood samples for measurement of free T_4, r-T_3, and T_3 and TSH levels will be repeated at Control 1 (Day 0, 5 hours after the first application of Somatoline®) and Control 2 (Day 1, 24 hours after the first application of Somatoline®), and then again on Day 14 and Day 28 (End of Treatment [EOT]).

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory frequency and body temperature) will be assessed at each visit. A full medical examination will be repeated at the EOS.

In order to assess the systemic tolerability of the treatment with Somatoline® gel, on Day 0, Day 1, Day 14 and Day 28, EOT and EOS (Follow-up), women will be asked for any adverse event (AE) or any issue observed during the treatment, and the bilateral sites of drug application will be inspected for any local reaction (erythema, swelling and itching), which will be scored. Moreover, a diary will be given to the patients at Day 0 and the patients will be asked to daily score any sign of erythema, swelling and itching, at the application site.

Finally, a 12-lead ECG will be run at the Screening and repeated on Day 0 (5 hours after the first Somatoline® application), on EOT and EOS, to assess any potential systemic absorption of T_4 and related effects on cardiac activity.

After the EOT (Day 28), women will be followed for additional 14 days. During the follow-up period, no treatment with Somatoline® will be allowed.

On Day 42 (EOS), blood samples for measurement of free T_4, r-T_3, T_3 and TSH levels will be drawn. On the same Day, women will be asked for any AE or any issue observed during the treatment, and the bilateral sites of drug application will be inspected for any local reaction, which will be scored.

5 SELECTION OF POPULATION

5.1 SUBJECTS SELECTION

The study will be run according to a single-group, open design. Briefly, a group of 30 healthy Caucasian women, aged between 18 and 50 years, will be selected for the participation into the study from a larger group, taking into consideration a maximum 20% percentage of screen failures, during a Screening period of 15 days (Day -15 to Day 0).

5.2 INCLUSION CRITERIA

Healthy woman will be enrolled in the study if they meet all the following inclusion criteria:

- *Sex and age*: Adult women aged between 18 and 50 years;
- *Race*: Caucasian;
- *Body mass index (BMI)*: $18.5 > BMI \leq 30$ kg/m^2;
- *Vital signs*: systolic blood pressure (SBP) = 100-139 mmHg; diastolic blood pressure (DBP) = 50-89 mmHg; heart rate (HR) = 50-90 bpm, measured after 5 min of rest (sitting position);
- *Electrocardiogram (ECG)*: no clinically relevant abnormalities at ECG (12 leads);
- *Physical examination*: no clinically relevant abnormal physical findings;

- *Laboratory analyses*: no clinically relevant abnormal laboratory values indicative of physical illness;
- *Allergy*: no ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients or ß lactam antibiotics;
- *Medical history*: no history of anaphylaxis to drugs or allergic reactions in general, no relevant history of renal, hepatic, cardiovascular, respiratory, skin, haematological, endocrine, or neurological diseases that may interfere with the aim of the study, no history of gastric mucosal damages, no neoplasia, no medications during 2 weeks before the start of the study, including OTC ("over the counter");
- *Participation in another experimental trial*: no participation in the evaluation of any experimental drug within 3 months prior to screening;
- *Blood donors*: no blood donations during 3 months prior to this study;
- *Drug or alcohol history*: no history of drug, alcohol (< 1 drink/day for females, defined according to USDA Dietary Guidelines 2000) or tobacco abuse (< 10 cigarettes/day);
- *Pregnancy*: not pregnant or lactating;
- *Contraception*: fertile women willing to use barrier contraceptive methods;
- *Subjects' capability*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study;
- *ICF*: signed written ICF prior to inclusion in the study
- *Life-style:* Willingness of the subject to maintain a constant life style during the period of the study.

5.3 EXCLUSION CRITERIA

Women will be excluded from the study if they meet anyone of the following inclusion criteria:

- *Pregnancy*: pregnant or lactating women;
- *ECG*: clinically relevant abnormalities;
- *Physical findings*: clinically relevant abnormal physical findings which could interfere with the study objectives;
- *Laboratory analyses*: clinically relevant abnormal laboratory values indicative of physical illness;
- *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considered to potentially affect the outcome of the study;
- *Diseases*: relevant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine (in particular, thyroid), or neurological diseases, which may interfere with the aim of the study, history of gastric mucosal damages, neoplasia;
- *Contraceptive*: changes (early or suspension) of the use of contraceptive oestrogen-progestin in the last 4 weeks, and inability to take adequate contraception during the study;

- *Medications and diet*: any medication, including OTC, is forbidden during the screening period. Moreover:
    - In the 6 months before screening, any treatment with antithyroid drugs or any therapeutic use of iodine or iodine-containing medications (e.g., amiodarone, Somatoline®) is forbidden;
    - In the 6 months before screening, any diagnostic tests that led to the use of tracers, contrast agents containing iodine or iodine isotopes, is forbidden;
    - in the 4 weeks before screening, no changes in diet of foods containing iodine (e.g., iodized salt), or use disinfectants (e.g., betadine), detergents or any systemic or topical product containing iodine, including mouthwashes (e.g., Iodosan), toothpaste iodinated, douches, Lugol's solution;
    - In the 4 weeks before screening, any use of food supplements and herbal medicines;
    - a daily intake of iodized salt < 1,100 µg/day.
- *Investigative drug trials*: participation in the evaluation of any experimental drug within 3 months prior to the start of the study;
- *Blood donation*: blood donations during the 3 months prior to this study;
- *Drug, alcohol, tobacco*: history of drug, alcohol (> 1 drink/day for females, defined according to USDA Dietary Guidelines 2000) or tobacco abuse (> 10 cigarettes/day).

5.4 WITHDRAWAL OF SUBJECTS

Subjects will be free to withdraw from the study at any time without giving any reason. Subjects will be advised that if they requested to withdraw from the study at any time during the trial, this has no negative consequences.

The PI can also withdraw subjects from the trial if he deemed it appropriate for safety of subjects, for ethical reasons, or if he believes that the continuation of the study would be detrimental to the subjects' well-being. Subjects who withdraw will undergo a final medical evaluation.

Subjects can be withdrawn also for the following reasons:

- if an AE - including a concomitant illness - develops that is considered by the Investigator incompatible with the continuation of the study;
- if the administration of a drug which is not allowed by the exclusion criteria, becomes necessary;
- failure to comply with requirements of the protocol.

5.5 PREMATURE TERMINATION

For any subject discontinuing the study before scheduled, the Investigator will:

- ask the subject to undergo, whenever possible, the EOS visit to ascertain his/her health conditions and to perform the required blood sampling. The examination must verify that all values tested at pre-study have remained within a clinically acceptable range (not clinically relevant changes compared to screening);
- complete the CRF, reporting the date of termination, date and time of last dose administration and reason for study discontinuation;
- arrange for alternative medical care of the withdrawn subject, if necessary;

- enter in the CRF any follow-up, if the subject is withdrawn for an AE.

6 TREATMENTS

6.1 INVESTIGATIONAL MEDICINAL PRODUCT

Somatoline® gel is the investigational medicinal product (IMP) to be used in the clinical trial. The study medication characteristics are reported in Table 1.

TABLE 1 Study Medication Characteristics

STUDY MEDICATION CHARACTERISTICS	
Generic/Trade Name:	Somatoline® gel
Chemical Name:	l-Thyroxine
Formulation:	Gel
Strength:	10%
Dose regimen:	10 g gel (l-T_4 10 mg/escin 30 mg) on each thigh per day during the first 2 days (20 grams per day in total), followed by 5 grams per thigh (10 grams per day in total) until the end of a 4-week period
Route of administration:	Topical (cutaneous)
Storage Conditions:	Room temperature and humidity

6.2 DOSAGE AND ADMINISTRATION

In the course of the clinical trial, the women will be instructed to apply Somatoline® 10 g gel (l-T_4 10 mg/escin 30 mg) on each thigh per day during the first 2 days (20 grams per day in total), followed by 5 grams per thigh (10 grams per day in total) until the end of a 4-week period starting from the day the first dose was applied. The subjects have to apply the product and then massage the skin of the entire thigh for several minutes until completely absorbed. The dosage and administration way are consistent with the recommendations by the Investigator's Brochure. 2 dated 3rd July 2018.

6.3 PACKAGING AND LABELLING

All labels will include conditions for storage, lot number, and other information required by the ICH, and/or Annex 13, and all local regulations for investigational medications.

6.4 STORAGE AND ACCOUNTABILITY

The Investigator or designee must maintain an accurate record of receipt of shipment and dispensing of Sponsor-supplied study treatment in a drug accountability log. Accountability for Sponsor-supplied study treatment will be documented throughout the study and reconciled. All unused Sponsor-supplied study treatment must be returned to the site and the Sponsor will be responsible to collect the used and unused drug. It will be asked to the subjects to collect the used drug and bring it during the next control.

6.5 CONCOMITANT MEDICATIONS AND STUDY RESTRICTIONS

No dietary changes of iodine-containing food or changes in the use of iodine-containing disinfectants, detergents or mouthwash products will be allowed during the study. A maximum daily intake of iodized salt < 1,100 µg/day is allowed during the study.

6.6 PRECAUTIONS/OVERDOSAGE

The IMP will be applied topically (cutaneous) and, therefore, no issue of overdosage is expected.

6.7 TREATMENT ALLOCATION AND RANDOMISATION PROCEDURES

The study is open and there will be no randomization procedure.

6.8 EMERGENCY CODE AND UNBLINDING PROCEDURES

The study is open and no unblinding procedures are in place.

7 STUDY PROCEDURES

7.1 OVERALL STUDY SCHEDULE

The study will be run according to a single-group, open design. Briefly, a group of 30 healthy Caucasian women, aged between 18 and 50 years, will be selected for the participation into the study from a larger group, taking into consideration a maximum 15% percentage of SFs, during a screening period of 15 days (Day -15 to Day 0).

7.2 SCREENING (DAY -15 TO DAY 0)

The Screening period should last no more than 15 days (Day -15 to Day 0).

The women will be early informed about the purposes of the study and the risks related to the study participation. If they agree to participate, they will be consented with the most recently approved ICF, and then evaluated for their compliance to the inclusion and exclusion criteria in the course of a full physical examination.

Haematology, blood chemistry, plasma concentrations of TSH, urinalysis and ioduria will be performed, as well as a full virology and urine drug screening and a pregnancy test has to be performed. A 12-lead ECG will be run in order to check the heart functionality. Vitals signs (SBP, DBP, HR, RF, body temperature) will be recorded. Thyroid hormonal assessments will be possibly done at the same time (± 1 hour) consistently throughout the study. Recording to AEs will start as soon as the subject has signed the ICF.

No dietary changes of iodine-containing food or changes in the use of iodine-containing disinfectants, detergents or mouthwash products will be allowed during the study.

7.3 BASELINE (DAY 0)

After a medical visit (including vital signs) at Baseline (Day 0) has reconfirmed the eligibility criteria and a negative pregnancy test has been obtained, the women will be assessed again for plasma concentrations of T_4, T_3, rT_3 and TSH. Vitals signs (SBP, DBP, HR, RF, body temperature) will be recorded.

After these examinations, the women will be instructed to apply Somatoline® 10 g gel (l-T_4 10 mg/escin 30 mg) on each thigh per day during the first 2 days (20g per day in total), followed by 5g per thigh (10g per day in total) until

the end of a 4-week period starting from the day the first dose was applied. The subjects have to apply the product and then massage the skin of the entire thigh for several minutes until completely absorbed.

7.4 CONTROL 1 (DAY 0 – 5 HOURS AFTER THE FIRST APPLICATION)

Five hours after the first application of Somatoline®, the vital signs (SBP, DBP, HR, RF, body temperature) will be recorded. The two application sites of the skin will be inspected for any local reaction, which eventually will be scored. Again, the blood samples for measurement of free T_4, r-T_3, and T_3 and TSH levels will be collected. Then, if no AE has been recorded and no health issue is ongoing, the women will be left free to leave the clinical site.

7.5 CONTROL 2 (DAY 1 - 24 HOURS)

Twenty-four hours after the first application of Somatoline®, women will be asked to attend the clinical site again. The women will be asked for any AE or any issue observed during the treatment, and the bilateral sites of drug application will be inspected for any local reaction, which will be scored. The vital signs (SBP, DBP, HR, RF, body temperature) will be recorded. Blood samples for measurement of free T_4, r-T_3, and T_3 and TSH levels will be repeated. Then, if no AE has been recorded and no health issue is ongoing, the women will be left free to leave the clinical site.

7.6 CONTROL 3 (DAY 14)

Fourteen days after starting treatment with Somatoline®, the women will be asked to attend the clinical site again. The women will be asked for any AE or any issue observed during the treatment, and the bilateral sites of drug application will be inspected for any local reaction, which will be scored. The vital signs will be recorded. Blood samples for measurement of free T_4, r-T_3, and T_3 and TSH levels will be repeated at a standard time (8:00 a.m. ± 1 hour). Then, if no AE has been recorded and no health issue is ongoing, the women will be left free to leave the clinical site.

7.7 END OF TREATMENT (DAY 28)

Twenty-height days after starting treatment with Somatoline®, the women will be asked to attend the clinical site. The women will be asked for any AE or any issue observed during the treatment, and the bilateral sites of drug application will be inspected for any local reaction, which will be scored. The vital signs (SBP, DBP, HR, RF, body temperature) will be recorded. A 12-lead ECG will be run. Blood samples for measurement of free T_4, r-T_3, and T_3 and TSH levels will be repeated at a standard time (± 1 hour). Then, if no AE has been recorded and no health issue is ongoing, the women will be left free to leave the clinical site.

7.8 END OF STUDY (DAY 42)

At the end of the follow-up period, the women will be asked to attend the clinical site. The women will be asked for any AE or any issue observed during the treatment, and the bilateral sites of drug application will be inspected for any local reaction, which will be scored. The vital signs (SBP, DBP, HR, RF, body temperature) will be recorded. A 12-lead ECG will be run. Blood samples for measurement of free T_4, r-T_3, and T_3 and TSH levels will be repeated at a standard time ± 1 hour) and ioduria will be assessed.

8 OTHER STUDY MATERIAL

Besides medications, the following study material will be supplied to the clinical center:

- Final version of the study Protocol and Synopsis
- ICF
- CRF for each subject plus some spare copies
- Information Leaflet
- Subject's Card
- Subject's Diary for each subject plus some spare copies

On the Day 0, each woman will be provided with a Subject's Diary and she will be asked to score the following three symptoms:

- Erythema;
- Swelling;
- Itching;

at each day from Day 1 to Day 28, for each application site (right and left). Each symptom will be scored with a 4-point scale, from 0 = absent to 1 = mild, 2 = moderate and 3 = severe.

The women will be asked to complete the diary daily and to return the complete diary at the EOT. The women will be also provided with an information leaflet on how the IMP (Somatoline® gel) should be applied on the cutaneous surface of the right and left thighs.

9 MEASUREMENT OF EFFICACY AND SAFETY VARIABLES

9.1 PRIMARY EFFICACY VARIABLES

Blood samples for measurement of TSH concentrations will be collected during the Screening (Day -15 to Day 0), and free T_4, r-T_3, T_3 and TSH concentrations at Control 1 (Day 0 – Hour 5), Control 2 (Day 1), Control 3 (Day 14) and EOT (Day 28). The assessments will be repeated at EOS (Day 42) after a 28-day follow-up, during which no treatment will be performed. Apart from the Control 1 assessment, all blood samples will be collected at the same time of the day, with a time window of ± 1 hour.

9.2 SAFETY VARIABLES

Safety of the tested formulation will be evaluated based on the following assessments:

- Record of AEs, throughout the entire study duration;
- Record of local tolerability (application site) by the patients through the Subject's Diaries;
- Record of local tolerability (application site) by the investigators at the medical visits (Day 0, Day 1, Day 14, Day 28 and Day 42).

9.2.1 *Physical examination*

Full physical examinations will be performed at the Screening (Day -15 to Day 0), Baseline (Day 0), Day 42 (EOS). Information about the physical examination will be recorded by the Investigator in the source documentation at the clinical Site. Any abnormalities will be recorded in the CRF. Significant findings/illnesses, reported after the start of the study and which meet the definition of an AE, will be recorded in the CRF.

9.2.2 *Vital signs*

Subjects SBP/DBP, HR, RF and body temperature, will be measured by the Investigator or his/her deputy after 5 min of rest (sitting position). The measurements will be performed at:

- Screening (Day -15 to Day 0);
- Baseline (Day 1: pre-dose, and 5 hours post-dose);
- Day 1;
- Day 14;
- Day 28 (EOT);
- Day 42 (EOS).

9.2.3 *ECGs*

A 12-leads ECG will be performed at Screening, Day 28 (EOT) and Day 42 (EOS).

9.2.4 *Clinical laboratory assays*

Samples of blood (15 ml) and urine will be collected. The following laboratory analyses will be performed at Screening:

- **Hematology:** RBC, WBC and leukocyte differential count, platelet count, haemoglobin, MCV, MCH, MCHC, haematocrit;
- **Blood Chemistry:** total proteins, total bilirubin, alkaline phosphatase, AST, ALT, γ-GT, urea, creatinine, sodium, potassium, calcium, chloride, inorganic phosphorus, fasting glucose;
- **Urine drug screening**: presence of cannabinoids, opiates, cocaine, amphetamines, barbiturates, methadone and ecstasy;
- **Urinalysis:** Complete urinalysis and ioduria;
- **Virology:** HBs Ag, HCV Ab, HIV;
- **Thyroid:** TSH;
- **Pregnancy test.**

The following laboratory analyses will be performed at Baseline:

- **Thyroid**: T_4, T_3, rT_3 and TSH (T = 0);
- **Pregnancy test.**

The following laboratory analyses will be performed at Control 1, Control 2, Control 3, and EOT:

- **Thyroid**: T_4, T_3, rT_3 and TSH.

The following laboratory analyses will be performed at EOS:

- **Hematology:** RBC, WBC and leukocyte differential count, platelet count, haemoglobin, MCV, MCH, MCHC, haematocrit;
- **Blood Chemistry:** total proteins, total bilirubin, alkaline phosphatase, AST, ALT, γ-GT, urea, creatinine, sodium, potassium, calcium, chloride, inorganic phosphorus, fasting glucose;

- **Urinalysis:** complete urinalysis and ioduria;
- **Thyroid:** T_4, T_3, rT_3 and TSH.

9.2.5 *Local tolerability assessment, throughout the entire study duration*

Local tolerability of Somatoline® will be assessed by the Investigator and the subjects throughout the collection of data in the subject diary during the entire study duration.

The Investigator will assess the local tolerability at the application site (both sides, left and right) on Day 1 after 5 hours since the first application, Day 14, Day 28 and Day 42, by scoring (0-3) each of the following parameters (Table 2):

- Redness;
- Swelling;
- Hitching.

Table 2. Scores for the Investigator's assessment of redness, swelling and hitching.

Score	Severity
0	None
1	Mild
2	Moderate
3	Severe

10 ADVERSE EVENTS DESCRIPTION & REPORTING

10.1 DEFINITION OF ADVERSE EVENT

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

Adverse Drug Reaction (ADR)

An ADR is defined as "Any noxious and unintended response to a medicinal product related to any dose administered". The phrase "responses to a medicinal product" or "associated with the use of the medication," means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria:

a) Results in death

b) Is life threatening.

The term 'life threatening' in the definition refers to an event during which the subject was at risk of death at the time of the event. It does not refer to an event that, hypothetically, might have caused death if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization.

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

a. The admission results in a hospital stay of less than 12 hours

b. The admission is pre-planned (i.e., elective, or scheduled surgery arranged prior to the start of the study)

c. The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care)

However, it should be noted that invasive treatment during any hospitalization may fulfil the criterion of 'medically important' and as such may be reportable as an SAE, dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

c) Results in persistent or significant disability/incapacity

Disability means a substantial disruption of a person's ability to conduct normal life functions.

d) Is a congenital anomaly/birth defect;

e) Is another medically important serious event as judged by the investigator

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

An isolated laboratory abnormality is not reportable as an SAE unless the investigator assesses that the event meets standard International Conference on Harmonisation criteria for an SAE.

SUSAR

Suspected Unexpected Serious Adverse Reaction.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product or package insert/summary of product characteristics for a marketed medicinal product).

The term 'severity' is used here to describe the intensity of a specific event. This must be distinguished from the

term 'serious'. The expectedness of an adverse reaction is determined by the sponsor in the Reference Safety Information ('RSI'). This should be done from the perspective of events previously observed, not based on what might be anticipated from the pharmacological properties of a medicinal product.

For the present Study Protocol, the most recent update of the IB of the study medications is used as RSI.

10.2 TIME PERIOD, FREQUENCY, AND METHOD OF DETECTING AEs AND SAEs

SAEs that occur at any time after the inclusion of the subject in the study (defined as the time when the subject signs the ICF) up to 30 days after the subject completed or discontinued the study must be reported. The subject is considered to have completed the study EITHER after the completion of the last visit or contact (e.g., phone contact with the investigator or designee) (EOS), OR after the last dose of the study medication, whichever is later. The date of discontinuation is when a subject and/or investigator determines that the subject can no longer comply with the requirements for any further study visits or evaluations.

Additionally, to fulfil international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the patient consents to participate in the study until she/he is discharged.

Patients will be monitored at each schedule assessment at the site, at any contact with the subject during the study, and at the withdrawal visit, for the occurrence of AEs/SAEs.

10.3 RECORDING OF AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The PI will then record all relevant information regarding an AE/SAE on the appropriate section of the CRF. In case of SAE, the Investigator will fill in also the SAE Reporting Form.

10.4 ASSESSMENT OF AE RELATIONSHIP TO TREATMENT.

The PI must assess the relationship of any AE to the use of study drug, based on available information, by meaning as indicated in the following table (Table 3).

Table 3. Casual Attribution Guidance

Is the AE is suspected to be caused by the study drug based on facts, evidence, science-based rationales, and clinical judgment	
Yes	There is a plausible temporal relationship between the onset of the adverse event and administration of the drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and /or the adverse event follows a known pattern of response to the study drug; and/ or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
No	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an aetiology other than the study drug (e.g. pre-existing medical condition, underlying disease, intercurrent, illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

10.5 EXPEDITED REPORTING OF SAEs

All SAEs, whether or not deemed drug-related or expected, must be reported in writing by using the SAE Form by the PI within 24 hours (one working day) of first becoming aware of the event to:

- Email: farmacovigilanza@pharmades.it,
- Fax +39-055-7227014.

The report is made by the Investigator in writing by email and/or by fax, by meaning the form designated for SAE reporting (SAE Report Form).

10.6 FOLLOW-UP OF SAE/SADRs

After the initial SAE report, the PI is required to proactively follow each patient and provide further information on the patient's condition. All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

The PI will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

10.7 REPORTING OF SUBJECT DEATH

The death of any subject during the study or within 30 days of study completion (as defined above), regardless of the cause, must be reported within the same day of first becoming aware of the death.

10.8 REPORTING OF PREGNANCIES

A female patient must be instructed to stop taking the study medication and immediately inform the PI if she becomes pregnant during the study. The PI should report all pregnancy within 24 hours to the Sponsor using the Pregnancy Form. The PI should counsel the patient, discuss the risk of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring during the post-treatment follow-up period must also be reported.

10.9 SAFETY OBLIGATIONS OF THE SPONSOR

The Sponsor is responsible for the following (according to Directive 2001/20/EC; GCP Directive 2005/28/EU, D. Lgvo 211/2003; and Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01):

- recording of AEs;
- reporting of suspected unexpected serious adverse reactions ('SUSARs') to the national competent authority (through the Eudravigilance Clinical Trials Module) and the IEC.

In addition, the Sponsor will perform the annual safety reporting to the NCA and the IEC.

The sponsor will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the NCA concerned, and to the IEC, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

The Sponsor will assure that all other SUSARs shall be reported to the NCAs and IECs concerned as soon as

possible but within a maximum of 15 days of first knowledge by the sponsor.

The sponsor will keep detailed records of all AEs which are reported to him by the investigator or investigators. The documentation concerning safety information will be kept in a secure site by the Sponsor for at least 7 years.

11 DATA MANAGEMENT AND STATISTICAL ANALYSIS

11.1 DATA MANAGEMENT AND DATA QUALITY ASSURANCE

11.1.1 *Data collection / CRF*

The PI is responsible for ensuring that the clinical data required by the study protocol are carefully reported in the CRFs. He is also responsible for checking that the data reported in the CRFs correspond to those in the official files. To ensure legibility, the CRFs should be filled out in English, in block capitals with a ball-point pen (not pencil, felt tip or fountain pen). Any correction to the CRFs' entries must be carried out by the Investigator or a designated member of staff. Incorrect entries must not be covered with correcting fluid, or obliterated, or made illegible in any way. A single stroke must be drawn through the original entry. Corrections have to be dated and initialized. In the interests of completeness of data acquisition, the questions which are repeated in each section of the CRFs should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data.

CRFs will be completed and, after being signed by the Investigator, will be returned to the Sponsor after termination of the individual treatment and the final visit.

11.1.2 *Coding Dictionaries*

AEs, medical history and concomitant diseases will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Version of coding dictionaries will be stated in the study report.

11.2 STATISTICAL ANALYSIS

The data documented in this trial and the parameters measured will be compared and evaluated using classic descriptive statistics: mean, SD, CV (%), minimum and maximum values (for quantitative variables) and by frequencies (qualitative variables).

All results of statistical tests will be considered significant if inferior to 0.05 ($p<0.05$).

The statistical analysis will be performed using either SAS® version 9.4 for Windows® (SAS Institute Inc., Cary, North Carolina, United States).

11.2.1 *Statistical hypotheses*

The null hypothesis of statistical tests is:

$H_0 : \Delta = 0$ *the difference from baseline is equal to 0*;

and the alternative hypothesis is:

$H_1: \Delta \neq 0$ *the difference from baseline is not equal to 0*;

11.2.2 *Sample size*

Based on a prior experience conducted with a similar formulation (Certan et al. 2013) mean value of FT4 was assumed to be 11.0 ± 1.2 pg/mL and a sample size of 26 subjects was estimated to allow confirming the stability of said value during the study within confidence interval of ±0.7 (99% confidence interval). Assuming a dropout rate of 15% the decision was taken to enroll 30 subjects.

11.2.3 *Population for analysis*

Three populations will be defined for use in the descriptive and inferential statistical analyses: the Safety Population, the ITT Population and the PP Population.

- "Intention To Treat" Population (ITT population): the ITT population will include all enrolled subjects who received at least one dose of the study drug and had at least one post-dose assessment;
- "Per Protocol" Population (PP Population): the PP population will include all subjects who concluded the study without important protocol deviations or violations;
- "Safety Population": the population of interest for the safety assessments will consist of all subjects who will be enrolled and received at least one dose of the study drug.

11.2.4 *Missing data*

Data not available will be assessed as "missing values".

11.2.5 *Protocol deviations*

Any deviation(s) from protocol will be described and justified in the final report.

11.2.6 *Interim analysis*

No interim analysis is planned

11.2.7 *Statistical methods*

11.2.7.1 *Primary efficacy variables*

To evaluate the primary objective (the systemic bioavailability of l-T4 in female subjects with local cellulitis after repeated cutaneous of a gel formulation of Somatoline®), the mean of l-T4 at every blood sample will be calculated. The comparison of the means from baseline will be performed with ANOVA.

11.2.7.2 *Secondary efficacy variables*

To assess the systemic bioavailability of rT3, T3 and TSH, after repeated cutaneous application of a gel formulation of Somatoline® in female subjects with local cellulitis, ANOVA will be used.

11.2.7.3 *Safety and tolerability variables*

- **AEs**: The incidence of AEs/SAE will be evaluated by frequency tables providing, for each cross-classification and subcategory, the following frequencies:
  - Number and percentage of subjects reporting at least one AE/SAE.
  - Total number of AEs/SAEs observed.
- **Local tolerability** by both the investigator (medical visit) and the subject (diary). Frequency of scores will be presented by local tolerability tests (itching, redness and swelling).
- **Laboratory data.** Laboratory data will be summarized by presenting frequency tables of values falling outside normal ranges. Frequency of abnormalities will be compared by McNemar test, when applicable. Moreover, for each parameter the descriptive statistics and change versus baseline by time point will be reported.
- **ECGs.** ECGs will be summarized by presenting frequency tables of values falling outside normal ranges. Frequency of abnormalities will be compared by McNemar test, when applicable.
- **Vital signs.** descriptive statistics and change versus baseline by time point will be reported for each parameter. The values will be compared vs. pre-treatment values using ANOVA.
- **Physical Examination.** Physical examination will be presented by time point through descriptive statistics. Frequency of abnormalities will be presented and compared by McNemar test, when applicable.

11.3 BIOLOGICAL SAMPLES

Not Applicable

12 MONITORING AND ACCESS TO DATA

12.1 MONITORING

The study will be carried out in accordance with the most recent international GCP guidelines (ICH/GCP/R2), EU Directive and guidance and/or the local legislation on the conduct of clinical trials.
Manetti & Roberts has the responsibility of monitoring this study and has delegated this task to a CRO/Monitor. Study specific contracts have been issued and will be signed by both parties before the study initiation.
The monitor's duty is to aid the Investigator, and at the same time the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. In addition, the Monitor will explain, interpret and ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of the investigational medicinal product, the protocol, reporting responsibilities and validity of the data.
Details about the monitoring activities will be carefully described in the Monitoring Manual.

12.2 QUALITY CONTROL AND QUALITY ASSURANCE

The monitoring visits will be conducted by appropriate staff of the CRO. Adequate time for these visits should be made available by the PI. The study will be monitored by means of on-site visits and regular inspection of the CRF

with sufficient frequency to inspect the following:

- occurrence of AEs/SAEs;
- subject enrolment;
- compliance with the protocol procedures;
- the completeness and exactness of data entered in the CRF;
- verification against original source documents.

Data verification is required and will be done by direct comparison with source documents or by crosschecking with source documents, always considering data protection and medical confidentiality. In this respect, the PI assures the Sponsor of support at all times.

The PI agrees, by written consent to this protocol, to fully cooperate with compliance checks by allowing authorized individuals to have access to all documentation. In addition to the monitoring performed by the study monitor, the Sponsor could perform some quality control activities to verify the compliance with the study procedures and the ICH GLP guidelines. The study may also be audited/inspected by an independent body and/or authority.

13 ETHICAL AND REGULATORY ASPECTS

13.1 DECLARATION OF HELSINKI

The PI and Sponsor will ensure that this study is conducted in full compliance with Declaration of Helsinki (more recent version), the ICH guidelines, and the Italian laws, whichever affords the greatest protection to the study subject.

The approval of the study protocol by the relevant Competent Authorities and Independent Ethics Committees will be obtained before the start of the study.

The analytical assays will be carried out according to the General Principles of "OECD Good Laboratory Practices for testing of chemicals" C (81) 30 (final).

13.2 NCA AND IEC APPROVAL

Before staring the study, the Study Protocol and any other document used in the course of the study will be properly approved by the NCA and concerned IEC.

13.3 PROTOCOL AMENDMENTS

In order to obtain interpretable results, neither the Investigator nor the Sponsor will alter the study conditions agreed upon and set out in this protocol. Amendments should be made by mutual agreement between Investigator and Sponsor. Any amendment must be set out in writing, giving the reasons, and being signed by all concerned parties. The amendment becomes then part of the protocol.

All amendments will be sent to the NCA and IEC for approval. IEC will establish whether to submit them to the next IEC review prior to implementation (e.g. for changes increasing the risk for subjects) or to consider them as simple notifications (e.g. for minor protocol changes or when the changes involve only logistical or administrative aspects of the trial).

13.4 WRITTEN INFORMED CONSENT

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of ICF is required prior to administering study drug.

ICF is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IEC-approved, and the participant will be asked to read and review the document. The PI will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or think about it prior to agreeing to participate.

The participant will sign the ICF prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the ICF will be given to the participants for their records.

The ICF process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.5 INSURANCE

An insurance cover, in compliance with the article 3, paragraph 3 of Legislative Decree n° 211 of June 24, 2003, has been taken out in favour of subjects participating in the clinical trial. Cover is provided under the terms and conditions of the clinical trial.

The insurance policy is to grant specific cover in connection with the reimbursement of damages caused to the subjects by the clinical trial activities throughout the entire duration thereof, thus covering any civil liability of Investigator and Sponsor of the clinical trial, without excluding any damage which may be unintentionally caused by accident e/o be attributed to negligence, imprudence or inexperience, provided that they showed themselves within the periods

Following the terms of insurance, the Investigator and the Sponsor must strictly adhere to the study protocol and comply with the respective prevailing levels of scientific state of the art. The subjects must strictly adhere to the directions given by the Investigator. Subjects may undertake other medical treatments only under approval of the Investigator, except in case of emergencies.

13.6 CONFIDENTIALITY

By signing this protocol, the Investigator and the Site agree to keep all information provided by the Sponsor in strict confidentiality and to request similar confidentiality from his/her staff.

Trial documents provided by the Sponsor (protocols, Investigators' Brochures, CRFs and other materials) will be stored appropriately to ensure their confidentiality.

The information provided by the Sponsor to the Investigator and to the Site cannot be disclosed to others without direct written authorization from the Sponsor, except for the extent necessary to obtain the informed consent from the subjects wishing to participate in the trial.

14 LOCATION OF DATA

Before the initiation of the trial, during a Site Initiation Visit or an investigator's meeting, the monitor or a Sponsor's representative will review the protocol and Case Report Forms (CRF) together with the PI and his staff.

During the trial, the monitor will visit the Site regularly to check the completeness of subject records, the accuracy of entries in the CRFs, the adherence to the protocol and to GCP, the progress of enrolment, and to ensure that medication is being stored, dispensed and accounted for according to the specifications. The PI and key trial personnel must be available to assist the monitor during these visits.

The PI is responsible for completing the CRFs and the monitor is responsible for reviewing them, clarifying, and resolving any data queries. A copy of the CRFs is retained by the PI who must ensure that it is stored in a secure place with other trial documents, such as the protocol, the Investigator's Brochure and any protocol amendments.

Data on subjects collected on CRFs during the trial will be documented in an anonymous way. The subject will only be identified by the subject number. If, as an exception, it becomes necessary to identify a subject for safety or regulatory reasons, the monitor, the Sponsor and the PI will be bound to keep this information confidential.

The PI must keep source documents for each subject in the trial. All information on CRFs must be traceable to these source documents, which are generally stored in the subject's medical file. The source documents should contain all demographic and medical information, including laboratory data, ECGs etc., as well as the original signed ICF which should indicate the trial number and title of the trial.

Trial essential documents must be retained by the Investigator as long as needed to comply with national and international regulations. Essential documents include all those mentioned under ICH GCP Guidelines. The Investigator agrees to adhere to the document-retention procedures by signing the protocol.

15 REPORTING

A Clinical Study Report (CSR) will by prepared by Sponsor or delegate according to ICH topic E3 guidelines. The report will include a thorough description of the relevant methods, a discussion of the results, and a list of all the measurements.

A draft of the clinical study report will be submitted to the PI for comments. After receiving the comments, a final report will be issued. Any subsequent modification will be considered as an amendment to the final study report or a new version. The PI's agreement and signature will be obtained, and a copy will be provided to the Investigator. The signed original of the final report will remain with the Sponsor. The PI will receive a copy of the final report. At the end of the trial the Sponsor should provide the IEC and NCA with a summary of the clinical trial report.

16 PUBLICATION POLICY

By signing this protocol, all the partners agree that the scientific results that emerge from this study are the property of the Sponsor.

The Sponsor agrees in principle that the study results can be the subject of a scientific paper. However, no unpublished information contained herein, as well as no information received from the Sponsor for the purposes of this study, may be disclosed to any third party without the prior written approval of the Sponsor.

No data will be used for presentation at scientific meetings and/or publication in scientific journals before six months after the final study report has been agreed, signed and issued. The Sponsor reserves the right to use the results obtained as documentary and scientific backing in proceedings regarding the Health Authorities and/or for updating their own staff.

17 RESPONSIBILITIES

17.1 SPONSOR

The responsibilities of the Investigators are those considered in ICH GCP (E6R2). By signing this protocol, the PI states that he/she has been adequately informed regarding all aspects of the clinical trial. He/she accepts to follow all the specified procedures as described in the protocol and to comply with all the requirements therein.

Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni, Calenzano, Firenze (Italy).

- Sponsor Study Manager: Cristina Sabatini, Regulatory Affairs
- Tel: +39-055-8835320; Fax: +39-055-8835486; e-mail: csabatini@manettiroberts.it

17.2 CLINICAL CENTER

Clinical Pharmacology Centre for Drug Experimentation, University Hospital, via Roma, 67 - 56126 Pisa.

- PI: Dr Giovanni Gori.
- Tel: +39-050-993240; Fax: +39-050-993240; e-mail: giovannigori.gori@gmail.com.

17.3 CRO

CROnos Ricerche Cliniche srl, via Tonale, 22, 20125 Milano Italy

- Project manager: Dr. Elisabetta Di Martino
- Mobile: +39-345-9966300; e-mail: edimartino@cronos.srl

18 REFERENCES

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19 APPENDICES

19.1 APPENDIX I : SAMPLE OF STUDY MEDICATION LABELS

19.1.1 PRIMARY PACKAGING

Società Italo Britannica L. Manetti –
H. Roberts & C. per Azioni
Tel. 0558835320

FLACONE A

Levotiroxina 0.1% Escina 0.3%
Flacone airless da 250 g Gel per applicazione topica
USO CUTANEO
Studio N. SOMAGEL
EudraCT N. 2018-002380-26

Lotto clinico:
Scadenza:

Soggetto N. |__|__|__|
Ad esclusivo uso sperimentale.

Società Italo Britannica L. Manetti –
H. Roberts & C. per Azioni
Tel. 0558835320

FLACONE B

Levotiroxina 0.1% Escina 0.3%
Flacone airless da 250 g Gel per applicazione topica
USO CUTANEO
Studio N. SOMAGEL
EudraCT N. 2018-002380-26

Lotto clinico:
Scadenza:

Soggetto N. |__|__|__|
Ad esclusivo uso sperimentale.

19.1.2 SECONDARY PACKAGING

Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni,
Via Pellicceria, 8 Firenze - Tel. 0558835320

Sperimentatore: Dott. Giovanni Gori
Centro di farmacologia clinica per la sperimentazione dei farmaci
Edificio 8 "Clinica Medica G. Monasterio"
Stabilimento di Santa Chiara
Via Roma 67 – Pisa. Tel. 050/993240

Levotiroxina 0.1% Escina 0.3%
Flacone airless da 250 g Gel per applicazione topica
USO CUTANEO
Studio N. SOMAGEL
EudraCT N. 2018-002380-26

Soggetto N. |__|__|__|

Lotto clinico: Scadenza:

Istruzioni per l'uso:
4 erogazioni corrispondono a 10 g di prodotto
Applicare il prodotto sulle cosce.
Applicare localmente 20 g di prodotto al giorno (pari a 8 erogazioni) per i primi due giorni, successivamente 10 g di prodotto (pari a 4 erogazioni) al giorno o a giorni alterni.
Per i primi due giorni 4 erogazioni per ogni coscia, per i giorni successivi 2 erogazioni per coscia.
Per ottenere 1 erogazione spingere fino in fondo la pompetta dosatrice.

Ad esclusivo uso sperimentale.
Questo medicinale non richiede alcuna condizione particolare di conservazione.
Non usi questo medicinale dopo la data di scadenza che è riportata sulla scatola dopo SCAD.
La data di scadenza si riferisce all'ultimo giorno di quel mese.
Tenere fuori dalla vista e dalla portata dei bambini.

Tear off label (to be attached on the Accountability Form)

Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni
Tel. 0558835320
Sperimentatore: Dott. Giovanni Gori
Levotiroxina 0.1% Escina 0.3% per uso cutaneo
Soggetto N. |__|__|__|
Lotto clinico:
Scadenza:
Ad esclusivo uso sperimentale.

19.2 APPENDIX II: SAMPLE OF SUBJECT CARD

SUBJECT CARD

Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni
Tel. 0558835320
Studio SOMAGEL
EudraCT N. 2018-002380-26

Soggetto (Screening) N. |__|__|__|

Dottor Giovanni Gori
Centro di farmacologia clinica per la sperimentazione dei farmaci
Edificio 8 "Clinica Medica G. Monasterio"
Stabilimento di Santa Chiara Via Roma 67 - Pisa
Tel: 050/993240
Email: giovannigori.gori@gmail.com

16 APPENDICES

16.1 STUDY INFORMATION

16.1.2 Sample case report form

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	MANETTI & ROBERTS

CASE REPORT FORM

Study Code: Somagel

EudraCT Number: 2018-002380-26

Title: Single-group, open study on the systemic bioavailability, safety, local tolerability and efficacy of a new gel formulation of Somatoline® in 30 healty women.

Experimental Centre

Clinical Pharmacology Centre for Drug Experimentation
University Hospital of Pisa

Screening No.	|___|___|___|

CONFIDENTIALITY

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

SCREENING PERIOD
DAY – 15 TO DAY 0

Date

|__|__||__|__||__|__|__|__|
dd/mm/yyyy

Date of Subject's IC Signature |___|___||___|___||___|___|___|___|
dd/mm/yyyy

SUBJECT'S DEMOGRAPHY

Gender ☐ Male ☐ Female * → *If "Male", do not include in the study*

Date of Birth |___|___||___|___||___|___|___|___|
dd/mm/yyyy

Height (cm) |__|__|__| **Weight** (kg) |__|__|__|.|__|

BMI* (kg/m^2) |__|__|.|__|__| * → *If BMI <18.5 or ≥ 30.0 kg/m^2, do not include in the study*

Race*: ☐ Caucasian ☐ Other *(Specify)*: _____
* → *If "Other", do not include in the study*

VITAL SIGN

Subject has to rest in a sitting position for 5 minutes.

Sitting blood pressure *(mmHg)*		**Heart rate** *(bpm)*	**Respiratory Frequency** *(breaths per minute)*	**Body temperature** *(°C)*
Systolic *100 – 139**	Diastolic *50 – 89**	*50-90 **	*12-18*	*36.0 - 37.5*
|__|__|__|	|__|__|__|	|__|__|__|	|__|__|	|__|__|.|__|

* → *If out of normal range, do not include in the study and comment* .....

.....

CONCOMITANT MEDICATION

Has the subject taken any medication within the last two weeks, including OTC ("Over The Counter")?

☐ No ☐ Yes → *If "Yes", do not include to the study and complete "Concomitants Medication section at the end of the CRF"*

GENERAL MEDICAL HISTORY

Did the Subject participated in the evaluation of any experimental drug within 3 months prior to screening? ☐ No ☐ Yes → *If "Yes", do not include to the study*

Has the Subject had any condition which required hospitalization in the past, or chronic conditions that require or have required treatment? *Please, fill in the table below*

	NO	YES	*If "YES", please specify details*	Still present
Respiratory system	☐	☐		☐
Circulatory system	☐	☐		☐
Hematopoietic/lymphatic system	☐	☐		☐
Alimentary tract	☐	☐		☐
Nervous system	☐	☐		☐
Musculoskeletal system	☐	☐		☐
Genito/urinary system	☐	☐		☐
Endocrine/metabolic system	☐	☐		☐
Thyroid Disorders	☐	☐		☐
Allergic/immunologic system	☐	☐		☐
Genetic disorder	☐	☐		☐
Psychiatric disorder	☐	☐		☐
Integumentary system	☐	☐		☐
Gastrointestinal tract	☐	☐		☐
Other	☐	☐		☐

Additional Comments .....

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PHYSICAL EXAMINATION

	Normal	Abnormal		NA	**If "Abnormal CR", do not include in the study and fill below*
		NCR	CR*		
General conditions	☐	☐	☐	☐	

Nutrition condition	☐	☐	☐	☐	
Circulatory system	☐	☐	☐	☐	
Respiratory system	☐	☐	☐	☐	
Abdomen	☐	☐	☐	☐	
Throat and lymph nodes	☐	☐	☐	☐	
Skin	☐	☐	☐	☐	
Other	☐	☐	☐	☐	

Additional Comments .....

.....

ELECTROCARDIOGRAM (12-LEADS ECG)

Planned time	**Actual time** *(hh:mm)*	*Archive in Source Documents ECG printout*
Pre-dose	|__|__|:|__|__|	

ECG assessment
☐ Normal
☐ Abnormal NCR
☐ Abnormal CR → *If ticked, do not include in the study and comment below*

Comments .....

.....

.....

LABORATORY RESULTS: BLOOD

Archive all clinical laboratory results in Source Documents

Date/Hour of sample taken \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| *dd/mm/yyyy* \|__\|__\|:\|__\|__\| *hh/min*

HAEMATOLOGY

Analysis	**Value**	**Unit**	**Normal**	**Abnormal**	
				NCR	**CR**
Hcb		g/dL	☐	☐	☐
Hct		%	☐	☐	☐

RBC		$10^6/\mu L$	☐	☐	☐
WBC		$10^3/\mu L$	☐	☐	☐
Neutrophils		$10^3/\mu L$	☐	☐	☐
Lymphocytes		$10^3/\mu L$	☐	☐	☐
Monocytes		$10^3/\mu L$	☐	☐	☐
Basophils		$10^3/\mu L$	☐	☐	☐
Eosinophils		$10^3/\mu L$	☐	☐	☐
PLT		$10^3/\mu L$	☐	☐	☐
MCV		fL	☐	☐	☐
MCH		pg	☐	☐	☐
MCHC		g/dL	☐	☐	☐

BLOOD CHEMISTRY

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
Total proteins		g/dL	☐	☐	☐
Total bilirubin		mg/dL	☐	☐	☐
ALT		U/L	☐	☐	☐
AST		U/L	☐	☐	☐
γ-GT		U/L	☐	☐	☐
Na^+		mEq/L	☐	☐	☐
K^+		mEq/L	☐	☐	☐
Cl^-		mEq/L	☐	☐	☐
Ca^{++}		mg/dL	☐	☐	☐
Urea		mg/dL	☐	☐	☐
Alkaline phosphatase		U/L	☐	☐	☐
Creatinine		mg/dL	☐	☐	☐
Inorganic phosphorus		mg/dL	☐	☐	☐
Fasting glucose		mg/dL	☐	☐	☐

Has the subject undertaken any blood donation on the three months prior to the beginning of the study? SI ☐ NO ☐ *If "**Yes**", do not include in the study*

VIROLOGY *Archive all clinical laboratory results in Source Documents*

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
HBs Ag		S/CO	☐	☐	☐
HCV ab		S/CO	☐	☐	☐
HIV		S/CO	☐	☐	☐

LABORATORY RESULTS: URINALYSIS *Archive all clinical laboratory results in Source Documents*

Date/Hour of sample taken |__|__||__|__||__|__|__|__| |__|__|:|__|__|
dd/mm/yyyy *hh/min*

Urinalysis ☐ Normal

☐ Abnormal NCR

☐ Abnormal CR → *If "Abnormal CR", do not include in the study*

IODURIA RESULTS *Archive all clinical laboratory results in Source Documents*

Date/Hour of sample taken |__|__||__|__||__|__|__|__| |__|__|:|__|__|
dd/mm/yyyy *hh/min*

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
Ioduria		ppm	☐	☐	☐

If "Abnormal CR", do not include in the study

ENDOCRINOLOGY *Archive all clinical laboratory results in Source Documents*

Date/Hour of sample taken |__|__||__|__||__|__|__|__| |__|__|:|__|__|
dd/mm/yyyy *hh/min*

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
TSH		mUI/L	☐	☐	☐

If "Abnormal CR", do not include in the study

ALCOHOL CONSUMPTION

Alcoholemic Test ☐ Negative ☐ Positive → *If "Positive" do not include to the study*

Does the Subject consume alcohol every day?

☐ No ☐ Yes → *If "Yes" is ticked, please fill below*

Beer ☐ None ☐ ⭘ 680g
☐ > 680g → *If ticked, do not include in the study*

Wine ☐ None ☐ ⭘ 280g
☐ > 280g → *If ticked, do not include in the study*

Spirit (40%) ☐ None ☐ ⭘ 85g
☐ > 85g → *If ticked, do not include in the study*

NICOTINE CONSUMPTION

Does the Subject currently use nicotine products?

☐ Yes - tobacco abuse < 10 cigarettes/day

☐ Yes - tobacco abuse > 10 cigarettes/day → *If "Yes", do not include in the study*

☐ No → *If "No", please fill below:*

☐ Never used ☐ Ex-user, |__|__| cigarettes/day

RESULT OF URINE DRUG SCREEN

☐ Negative ☐ Positive → *If "Positive", do not include in the study*

Presence of:

☐ cannabinoids ☐ cocaine ☐ amphetamines ☐ ecstasy

☐ opiates ☐ methadone ☐ barbiturates

RESULT OF PREGNANCY TEST

☐ NA * ☐ Negative ☐ Positive→ *If "Positive", do not include in the study*

* → *If "NA" is ticked, specify:* ☐Male ☐ Other**

** → *If "Other" is ticked, please comment:*_____

CONTRACEPTION: Is the subject willing to abstain from any sexual intercourse or use one of the acceptable contraception methods from the time of the first dosing until the completion of the examination at the end of the study (barrier methods with spermicide)?

☐ Yes ☐ No → *If "No" is ticked, do not include in the study*

SUBJECT ELIGIBILITY FOR THE CLINICAL TRIAL

	INCLUSION CRITERIA	YES	NO
1	*Sex and age*: Adult women aged between 18 and 50 years	☐	☐
2	*Race*: Caucasian	☐	☐
3	*Body mass index (BMI)*: 18,5 > BMI ≤ 30 kg/m^2	☐	☐
4	*Vital signs*: systolic blood pressure (SBP) 100-139 mm Hg and diastolic blood pressure (DBP) 50-89 mmHg; heart rate (HR) 50-90 bpm, measured after 5 min of rest (sitting position)	☐	☐
5	*Electrocardiogram (ECG)*: no clinically relevant abnormalities at ECG (12 leads)	☐	☐
6	*Physical examination*: no clinically relevant abnormal physical findings	☐	☐

7	*Laboratory analyses:* clinically relevant abnormal laboratory values indicative of physical illness	☐	☐
8	*Allergy*: no ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients or beta lactam antibiotics	☐	☐
9	*Medical history:* no history of anaphylaxis to drugs or allergic reactions in general, no relevant history of renal, hepatic, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study, no history of gastric mucosal damages, no neoplasia, no medications during 2 weeks before the start of the study, including OTC ("over the counter")	☐	☐
10	*Participation in another experimental trial:* no participation in the evaluation of any experimental drug within 3 months prior to screening	☐	☐
11	*Blood donors*: no blood donations during 3 months prior to this study	☐	☐
12	*Drug or alcohol history*: no history of drug, alcohol (< 1 drink/day for females, defined according to USDA Dietary Guidelines 2000) or tobacco abuse (< 10 cigarettes/day)	☐	☐
13	*Pregnancy:* not pregnant or lactating	☐	☐
14	*Contraception:* fertile women willing to use barrier contraceptive methods	☐	☐
15	*Subjects' capacity:* ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study	☐	☐
16	*ICF*: signed written ICF prior to inclusion in the study	☐	☐
17	*Life-style*: Willingness of the subject to maintain a constant life style during the period of the study	☐	☐

→ *If "No", do not include in the study and comment* .....

EXCLUSION CRITERIA		**YES**	**NO**
1	*Pregnancy:* pregnant or lactating women	☐	☐
2	*ECG:* clinically relevant abnormalities	☐	☐
3	*Physical findings*: clinically relevant abnormal physical findings which could interfere with the study objectives	☐	☐
4	*Laboratory analyses*: clinically relevant abnormal laboratory values indicative of physical illness	☐	☐
5	*Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study	☐	☐
6	*Diseases*: relevant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine (in particular, thyroid) or neurological diseases, which may interfere with the aim of the study, history of gastric mucosal damages, neoplasia	☐	☐
7	*Contraceptive:* changes (early or suspension) of the use of contraceptive oestrogen-progestin in the last 4 weeks, and inability to take adequate	☐	☐

	contraception during the study		
8	*Medications and diet*: any medications, including OTC, is forbidden during the screening period. Moreover: • In the 6 months before screening, any treatment with antithyroid drugs or any therapeutic use of iodine or iodine-containing medications (e.g., amiodarone, Somatoline®) is forbidden • In the 6 months before screening, any diagnostic tests that led to the use of tracers, contrast agents containing iodine or iodine isotopes, is forbidden • in the 4 weeks before screening, no changes in diet of foods containing iodine (e.g., iodized salt), or use disinfectants (e.g., betadine), detergents or any systemic or topical product containing iodine, including mouthwashes (e.g., Iodosan), toothpaste iodinated, douches, Lugol's solution • In the 4 weeks before screening, any use of food supplements and herbal medicines • a daily intake of iodized salt < 1,100 µg/day.	☐	☐
9	*Investigative drug trials*: participation in the evaluation of any experimental drug within 3 months prior to the start of the study;	☐	☐
10	*Blood donation*: blood donations during the 3 months prior to this study;	☐	☐
11	*Drug, alcohol, tobacco*: history of drug, alcohol [> 1 drink/day for females defined according to USDA Dietary Guidelines 2000] or tobacco abuse (> 10 cigarettes/day).	☐	☐

→ *If "Yes", do not include in the study and comment* .....

.....

INVESTIGATOR CONFIRMATION OF ELIGIBILITY

If all inclusion and none of exclusion criteria are met, subject is enrolled into the study

Is the Subject eligible for enrolment?

☐ Yes ☐ No → *If "No", please complete "SCREENING FAILURE" section below*

Date |__|__||__|__||__|__|__|__| *dd/mm/yyyy*

Investigator's name .....

Investigator's signature .....

SCREENING FAILURE

☐ Screening Failure Withdrawal Date |__|__||__|__||__|__|__|__| *dd/mm/yyyy*

Primary Reason for Withdrawal *(please report main reason)*:

- ☐ Non-Fulfilment of Inclusion Criteria And/Or Exclusion Criteria
- ☐ Adverse Event
- ☐ Withdrawal by Patient
- ☐ Other, *please specify in comments section below*

Comments: .....

.....

.....

BASELINE VISIT
DAY 0 Before Dosing

Visit Date

|__|__||__|__||__|__|__|__|
dd/mm/yyyy

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**BASELINE** **DAY 0 – Before dosing**

REVIEW OF CLINICAL SYMPTOMS

Has the subject reported any new symptom since the screening visit?

☐ No ☐ Yes → *If "Yes", please comment below*

Comments: .....

.....

TRIAL RESTRICTION

Has the subject complied with all study restrictions?

☐ Yes ☐ No → *If "No", do not include in the study and comment below*

Comments: .....

.....

ADVERSE EVENT

Have any Adverse Events (AE) occurred?

☐ No ☐ Yes → *If "**Yes**", complete "Adverse Events Section" at the end of CRF*

CONCOMITANT MEDICATION

Has the subject taken any medication within the last two weeks?

☐ No ☐ Yes → *If "**Yes**", complete "Concomitants Medication" section at the end of CRF*

RESULT OF PREGNANCY TEST

☐ NA * ☐ Negative ☐ Positive→ *If "Positive", do not include in the study*

* → *If "NA" is ticked, specify:* ☐Male ☐ Other**

** → *If "Other" is ticked, please comment*:_____

CONTRACEPTION: Is the subject willing to abstain from any sexual intercourse or use one of the acceptable contraception methods from the time of the first dosing until the completion of the examination at the end of the study (barrier methods with spermicide)?

☐ Yes ☐ No → *If "No" is ticked, do not include in the study*

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	**BASELINE** **DAY 0 – Before dosing**

VITAL SIGN

Subject has to rest in a sitting position for 5 minutes.

Sitting blood pressure *(mmHg)*		**Heart rate** *(bpm)*	**Respiratory Frequency** *(breaths per minute)*	**Body temperature** *(°C)*
Systolic *100 – 139**	Diastolic *50 – 89**	*50-90 **	*12-18*	*36.0 - 37.5*
|__|__|__|	|__|__|__|	|__|__|__|	|__|__|	|__|__|.|__|

** → If out of normal range, please comment* .....

.....

PHYSICAL EXAMINATION

	Normal	**Abnormal**		**NA**	***If "Abnormal CR", do not include in the study and fill below***
		NCR	**CR***		
General conditions	☐	☐	☐	☐	
Nutrition condition	☐	☐	☐	☐	
Circulatory system	☐	☐	☐	☐	
Respiratory system	☐	☐	☐	☐	
Abdomen	☐	☐	☐	☐	
Throat and lymph nodes	☐	☐	☐	☐	
Skin	☐	☐	☐	☐	
Other	☐	☐	☐	☐	

Additional Comments .....

ENDOCRINOLOGY

Archive all clinical laboratory results in Source Documents.

Date/Hour of sample taken \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| \|__\|__\|:\|__\|__\|
dd/mm/yyyy *hh/min*

Analysis	**Value**	**Unit**	**Normal**	**Abnormal**	
				NCR	**CR**
TSH		mUI/L	☐	☐	☐
Free T4		ng/dL	☐	☐	☐
r-T3			☐	☐	☐
T3		µg/L	☐	☐	☐

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**BASELINE** **DAY 0 – Before dosing**

INVESTIGATOR CONFIRMATION OF ELIGIBILITY

Eligibility of Subject is confirmed by the Investigator? * ☐ Yes ☐ No

** If "**No**" is ticked, please fill "SUBJECT'S COMPLETION OF THE STUDY OR PREMATURE DISCONTINUATION" section in "End of Study" Visit, If "**Yes**" is ticked, please complete below*

Date |__|__||__|__||__|__|__|__|
dd/mm/yyyy

Investigator's name .....

Investigator's signature .....

TREATMENT ADMINISTRATION

Please attach IMP label on the "Drug accountability Form"

Batch number |_____|

Date/Time of administration |__|__||__|__||__|__|__|__| |__|__|:|__|__|
dd/mm/yyyy hh:mm

CONTROL 1

DAY 0

5 hours after dosing

Visit Date

|__|__||__|__||__|__|__|__|

dd/mm/yyyy

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	**CONTROL 1** **DAY 0 – 5 hours after dosing**

ENDOCRINOLOGY *Archive all clinical laboratory results in Source Documents*

Date/Hour of sample taken |__|__||__|__||__|__|__|__| *dd/mm/yyyy* |__|__|:|__|__| *hh/min*

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
TSH		mUI/L	☐	☐	☐
Free T4		ng/dL	☐	☐	☐
r-T3			☐	☐	☐
T3		µg/L	☐	☐	☐

VITAL SIGN *Subject has to rest in a sitting position for 5 minutes*

Sitting blood pressure *(mmHg)*		Heart rate *(bpm)*	Respiratory Frequency *(breaths per minute)*	Body temperature *(°C)*
Systolic *100 – 139**	Diastolic *50 – 89**	*50-90 **	*12-18*	*36.0 - 37.5*
|__|__|__|	|__|__|__|	|__|__|__|	|__|__|	|__|__|.|__|

** → If out of normal range, please comment* .....

.....

LOCAL TOLERABILITY ASSESSED BY INVESTIGATOR

Zone	Local Tolerability				
Right thigh	Redness:	0☐	1☐	2☐	3☐
	Swelling:	0☐	1☐	2☐	3☐
	Itching:	0☐	1☐	2☐	3☐
Left thigh	Redness:	0☐	1☐	2☐	3☐
	Swelling:	0☐	1☐	2☐	3☐
	Itching:	0☐	1☐	2☐	3☐

0: None 1: Mild 2: Moderate 3: Severe

ADVERSE EVENT

Have any Adverse Events (AE) occurred?

☐ No ☐ Yes → *If "**Yes**", complete "Adverse Events Section" at the end of CRF*

CONTROL 2
DAY 1
24 hours after dosing

Visit Date

|__|__||__|__||__|__|__|__|
dd/mm/yyyy

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**CONTROL 2** **DAY 1 – 24 hours after dosing**

ENDOCRINOLOGY

Archive all clinical laboratory results in Source Documents

Date/Hour of sample taken |__|__||__|__||__|__|__|__| *dd/mm/yyyy* |__|__|:|__|__| *hh/min*

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
TSH		mUI/L	☐	☐	☐
Free T4		ng/dL	☐	☐	☐
r-T3			☐	☐	☐
T3		µg/L	☐	☐	☐

VITAL SIGN

Subject has to rest in a sitting position for 5 minutes.

Sitting blood pressure (mmHg)		Heart rate (bpm)	Respiratory Frequency (breaths per minute)	Body temperature (°C)
Systolic *100 – 139**	Diastolic *50 – 89**	*50-90 **	*12-18*	*36.0 - 37.5*
|__|__|__|	|__|__|__|	|__|__|__|	|__|__|	|__|__|.|__|

* → *If out of normal range, please comment* .....

.....

LOCAL TOLERABILITY ASSESSED BY INVESTIGATOR

Zone	Local Tolerability				
Right thigh	Redness:	0☐	1☐	2☐	3☐
	Swelling:	0☐	1☐	2☐	3☐
	Itching:	0☐	1☐	2☐	3☐
Left thigh	Redness:	0☐	1☐	2☐	3☐
	Swelling:	0☐	1☐	2☐	3☐
	Itching:	0☐	1☐	2☐	3☐

0: None 1: Mild 2: Moderate 3: Severe

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**CONTROL 2** **DAY 1 – 24 hours after dosing**

CONCOMITANT MEDICATION

Has the subject taken any medication since the last visit?

☐ No ☐ Yes → *If "Yes", complete "Concomitants Medication section at the end of CRF"*

ADVERSE EVENT

Have any Adverse Events (AE) occurred?

☐ No ☐ Yes → *If "**Yes**", complete "Adverse Events Section" at the end of CRF*

CONTROL 3
DAY 14+1

Visit Date

|__|__||__|__||__|__|__|__|
dd/mm/yyyy

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	**CONTROL 3** **DAY 14+1**

ENDOCRINOLOGY

Archive all clinical laboratory results in Source Documents

Date/Hour of sample taken |__|__||__|__||__|__|__|__| *dd/mm/yyyy* |__|__|:|__|__| *hh/min*

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
TSH		mUI/L	☐	☐	☐
Free T4		ng/dL	☐	☐	☐
r-T3			☐	☐	☐
T3		µg/L	☐	☐	☐

VITAL SIGN

Subject has to rest in a sitting position for 5 minutes.

Sitting blood pressure (mmHg)		Heart rate (bpm)	Respiratory Frequency (breaths per minute)	Body temperature (°C)
Systolic *100 – 139**	Diastolic *50 – 89**	*50-90 **	*12-18*	*36.0 - 37.5*
|__|__|__|	|__|__|__|	|__|__|__|	|__|__|	|__|__|.|__|

** → If out of normal range, please comment* .....

.....

LOCAL TOLERABILITY ASSESSED BY INVESTIGATOR

Zone	Local Tolerability				
Right thigh	Redness:	0☐	1☐	2☐	3☐
	Swelling:	0☐	1☐	2☐	3☐
	Itching:	0☐	1☐	2☐	3☐
Left thigh	Redness:	0☐	1☐	2☐	3☐
	Swelling:	0☐	1☐	2☐	3☐
	Itching:	0☐	1☐	2☐	3☐

0: None 1: Mild 2: Moderate 3: Severe

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**CONTROL 3** **DAY 14+1**

CONCOMITANT MEDICATION

Has the subject taken any medication since the last visit?

☐ No ☐ Yes → *If "Yes", complete "Concomitants Medication section at the end of CRF"*

ADVERSE EVENT

Have any Adverse Events (AE) occurred?

☐ No ☐ Yes → *If "Yes", complete "Adverse Events Section" at the end of CRF*

END OF TREATMENT
DAY 28+3

Visit Date

|__|__||__|__||__|__|__|__|
dd/mm/yyyy

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	**END OF TREATMENT** **DAY 28+3**

ENDOCRINOLOGY

Archive all clinical laboratory results in Source Documents

Date/Hour of sample taken |__|__||__|__||__|__|__|__| |__|__|:|__|__|
dd/mm/yyyy *hh/min*

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
TSH		mUI/L	☐	☐	☐
Free T4		ng/dL	☐	☐	☐
r-T3			☐	☐	☐
T3		µg/L	☐	☐	☐

VITAL SIGN

Subject has to rest in a sitting position for 5 minutes.

Sitting blood pressure (mmHg)		Heart rate (bpm)	Respiratory Frequency (breaths per minute)	Body temperature (°C)
Systolic *100 – 139**	Diastolic *50 – 89**	*50-90 **	*12-18*	*36.0 - 37.5*
|__|__|__|	|__|__|__|	|__|__|__|	|__|__|	|__|__|.|__|

** → If out of normal range, please comment* .....

.....

.....

LOCAL TOLERABILITY ASSESSED BY INVESTIGATOR

Zone	Local Tolerability				
Right thigh	Redness:	0☐	1☐	2☐	3☐
	Swelling:	0☐	1☐	2☐	3☐
	Itching:	0☐	1☐	2☐	3☐
Left thigh	Redness:	0☐	1☐	2☐	3☐
	Swelling:	0☐	1☐	2☐	3☐
	Itching:	0☐	1☐	2☐	3☐

0: None 1: Mild 2: Moderate 3: Severe

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**END OF TREATMENT** **DAY 28+3**

CONCOMITANT MEDICATION

Has the subject taken any medication since the last visit?

☐ No ☐ Yes → *If "Yes", complete "Concomitants Medication section at the end of CRF"*

ADVERSE EVENT

Have any Adverse Events (AE) occurred?

☐ No ☐ Yes → *If "Yes", complete "Adverse Events Section" at the end of CRF*

END OF STUDY
DAY 42

Visit Date

|__|__||__|__||__|__|__|__|
dd/mm/yyyy

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**END OF STUDY (Follow-Up)** **Day 42**

LABORATORY RESULTS: BLOOD

Archive all clinical laboratory results in Source Documents

Date/Hour of sample taken |__|__||__|__||__|__|__|__| *dd/mm/yyyy* |__|__|:|__|__| *hh/min*

HAEMATOLOGY

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
Hcb		g/dL	☐	☐	☐
Hct		%	☐	☐	☐
RBC		$10^6/\mu L$	☐	☐	☐
WBC		$10^3/\mu L$	☐	☐	☐
Neutrophils		$10^3/\mu L$	☐	☐	☐
Lymphocytes		$10^3/\mu L$	☐	☐	☐
Monocytes		$10^3/\mu L$	☐	☐	☐
Basophils		$10^3/\mu L$	☐	☐	☐
Eosinophils		$10^3/\mu L$	☐	☐	☐
PLT		$10^3/\mu L$	☐	☐	☐
MCV		fL	☐	☐	☐
MCH		pg	☐	☐	☐
MCHC		g/dL	☐	☐	☐

BLOOD CHEMISTRY

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
Total proteins		g/dL	☐	☐	☐
Total bilirubin		mg/dL	☐	☐	☐
ALT		U/L	☐	☐	☐
AST		U/L	☐	☐	☐
γ-GT		U/L	☐	☐	☐
Na^+		mEq/L	☐	☐	☐
K^+		mEq/L	☐	☐	☐
Cl^-		mEq/L	☐	☐	☐
Ca^{++}		mg/dL	☐	☐	☐
Urea		mg/dL	☐	☐	☐
Alkaline phosphatase		U/L	☐	☐	☐
Creatinine		mg/dL	☐	☐	☐
Inorganic phosphorus		mg/dL	☐	☐	☐
Fasting glucose		mg/dL	☐	☐	☐

LABORATORY RESULTS: URINALYSIS

Archive all clinical laboratory results in Source Documents

Date/Hour of sample taken |__|__||__|__||__|__|__|__| *dd/mm/yyyy* |__|__|:|__|__| *hh/min*

Urinalysis ☐ Normal

☐ Abnormal NCR

☐ Abnormal CR → *If "Abnormal CR", specify* _____

IODURIA RESULTS

Archive all clinical laboratory results in Source Documents

Date/Hour of sample taken |__|__||__|__||__|__|__|__| *dd/mm/yyyy* |__|__|:|__|__| *hh/min*

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
Ioduria		ppm	☐	☐	☐

ENDOCRINOLOGY

Archive all clinical laboratory results in Source Documents

Date/Hour of sample taken |__|__||__|__||__|__|__|__| *dd/mm/yyyy* |__|__|:|__|__| *hh/min*

Analysis	Value	Unit	Normal	Abnormal	
				NCR	CR
TSH		mUI/L	☐	☐	☐
Free T4		ng/dL			
r-T3					
T3		µg/L			

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**END OF STUDY (Follow-Up) Day 42**

ELECTROCARDIOGRAM (12-LEADS ECG)

T time *(hh:mm)*	*Archive ECG printout in Source Documents*
|__|__|:|__|__|	

ECG assessment

☐ Normal
☐ Abnormal NCR
☐ Abnormal CR → *If ticked, please comment below*

Comments .....

.....

VITAL SIGN

Subject has to rest in a sitting position for 5 minutes.

Sitting blood pressure *(mmHg)*		**Heart rate** *(bpm)*	**Respiratory Frequency** *(breaths per minute)*	**Body temperature** *(°C)*
Systolic *100 – 139**	Diastolic *50 – 89**	*50-90 **	*12-18*	*36.0 - 37.5*
|__|__|__|	|__|__|__|	|__|__|__|	|__|__|	|__|__|.|__|

* → *If out of normal range, please comment* .....

.....

PHYSICAL EXAMINATION

	Normal	Abnormal		NA	**If "Abnormal CR", do not include in the study and fill below*
		NCR	CR*		
General conditions	☐	☐	☐	☐	
Nutrition condition	☐	☐	☐	☐	
Circulatory system	☐	☐	☐	☐	
Respiratory system	☐	☐	☐	☐	
Abdomen	☐	☐	☐	☐	
Throat and lymph nodes	☐	☐	☐	☐	
Skin	☐	☐	☐	☐	
Other	☐	☐	☐	☐	

Additional Comments .....

.....

LOCAL TOLERABILITY ASSESSED BY INVESTIGATOR

Zone	Local Tolerability				
Right thigh	**Redness:**	0☐	1☐	2☐	3☐
	Swelling:	0☐	1☐	2☐	3☐
	Itching:	0☐	1☐	2☐	3☐
Left thigh	**Redness:**	0☐	1☐	2☐	3☐
	Swelling:	0☐	1☐	2☐	3☐
	Itching:	0☐	1☐	2☐	3☐

0: None 1: Mild 2: Moderate 3: Severe

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**END OF STUDY (Follow-Up)** **Day 42**

CONCOMITANT MEDICATION

Has the subject taken any medication since the last visit?

☐ No ☐ Yes → *If "Yes", complete "Concomitants Medication section at the end of CRF"*

ADVERSE EVENT

Have any Adverse Events (AE) occurred?

☐ No ☐ Yes → *If "Yes", complete "Adverse Events Section" at the end of CRF*

Treated Zone Events

Day	Zone	Treatment	Local Tolerability
Day 1 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 2 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 3 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 4 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**SUBJECT'S DIARY** **(Copy here from verified subject's diary)**

Day	Zone	Treatment	Local Tolerability
Day 5 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 6 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 7 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 8 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**SUBJECT'S DIARY** **(Copy here from verified subject's diary)**

Day	Zone	Treatment	Local Tolerability
Day 9 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 10 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 11 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 12 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**SUBJECT'S DIARY** **(Copy here from verified subject's diary)**

Day	Zone	Treatment	Local Tolerability
Day 13 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 14 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 15 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 16 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**SUBJECT'S DIARY** **(Copy here from verified subject's diary)**

Day	Zone	Treatment	Local Tolerability
Day 17 Date: |___|___|___| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 18 Date: |___|___|___| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 19 Date: |___|___|___| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 20 Date: |___|___|___| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**SUBJECT'S DIARY** **(Copy here from verified subject's diary)**

Day	Zone	Treatment	Local Tolerability
Day 21 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 22 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 23 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 24 Date: |__|__|__| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐

Day	Zone	Treatment	Local Tolerability
Day 25 Date: |___|___|___| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 26 Date: |___|___|___| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 27 Date: |___|___|___| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
Day	**Zone**	**Treatment**	**Local Tolerability**
Day 28 Date: |___|___|___| dd mm yy	**RIGHT THIGH**	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐
	LEFT THIGH	□ Yes □ No, Specify: _____ _____	**REDNESS:** 0☐ 1☐ 2☐ 3☐ **SWELLING:** 0☐ 1☐ 2☐ 3☐ **ITCHING:** 0☐ 1☐ 2☐ 3☐

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	**SUBJECT'S DIARY** **(Copy here from verified subject's diary)**

Health Conditions

Did the Subject completed Section 2 *"Eventi che riguardano il suo stato di salute"*?

☐ No ☐ Yes → *If "**Yes**" is ticked, please complete "Adverse Events" section at the end of CRF*

Concomitant Medications

Did the Subject completed Section 3 *"Medicinali Concomitanti"*?

☐ No ☐ Yes → *If "**Yes**" is ticked, please complete "Concomitants Medication" section at the end of CRF*

Subject's Diary Verification

Subject's Diary Verified by	**Name and Surname**	
	Signature	
	Date	|___|___|___| dd mm yy

SUBJECT'S COMPLETION OF THE STUDY OR PREMATURE DISCONTINUATION

Last day of participation in the study (including follow-up)

|___|___||___|___||___|___|___|___|
dd/mm/yyyy

Did the Subject complete the whole study? ☐ Yes ☐ No → *If "No", please fill below*

Primary Reason for Withdrawal (please report main reason):

☐ Adverse Event

☐ Serious Adverse Event

☐ Protocol Violation *Please specify below in comments*

☐ Withdrawal by Patient

☐ Other *Please specify below in comments*

Comments: .....

.....

.....

Date/time of discontinuation: |___|___||___|___||___|___|___|___| |__|__|:|__|__|
dd/mm/yyyy hh:mm

Additional Comments: .....

.....

CONCOMITANT MEDICATIONS

Related to:	Drug	Route	Dose	Unit	Indication	Start Date	End Date/ Ongoing
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	**CONCOMITANTS MEDICATIONS**

☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐
☐ AE n°__ ☐ SAE n°__ ☐ Medical History						|__|__|__|	|__|__|__| ☐

SOMAGEL PROTOCOL **SUBJECT NUMBER |___|___|___|**	**ADVERSE EVENTS**

ADVERSE EVENT NUMBER 1

Description AE/ADR: .....

.....

.....

Start date: |___|___||___|___||___|___|___|___|

Ongoing ☐ Yes ☐ No If **NO**, indicate Stop date|___|___||___|___||___|___|___|___|

SERIOUSNESS				CORRALATION				EXPECTEDNESS			
Serious*	☐	**Not Serious**	☐	**Correlated**	☐	**Not correlated**	☐	**Expected**	☐	**Unexpected**	☐

**If Serious you must complete the SAE/SADR Reporting form and the relative CRF section*

ADVERSE EVENT NUMBER 2

Description AE/ADR: .....

.....

.....

Start date: |___|___||___|___||___|___|___|___|

Ongoing ☐ Yes ☐ No If **NO**, indicate Stop date|___|___||___|___||___|___|___|___|

SERIOUSNESS				CORRALATION				EXPECTEDNESS			
Serious*	☐	**Not Serious**	☐	**Correlated**	☐	**Not correlated**	☐	**Expected**	☐	**Unexpected**	☐

**If Serious you must complete the SAE/SADR Reporting form and the relative CRF section*

ADVERSE EVENT NUMBER 3

Description AE/ADR: .....

.....

.....

Start date: |___|___||___|___||___|___|___|___|

Ongoing ☐ Yes ☐ No If **NO**, indicate Stop date|___|___||___|___||___|___|___|___|

SERIOUSNESS				CORRALATION				EXPECTEDNESS			
Serious*	☐	**Not Serious**	☐	**Correlated**	☐	**Not correlated**	☐	**Expected**	☐	**Unexpected**	☐

**If Serious you must complete the SAE/SADR Reporting form and the relative CRF section*

ADVERSE EVENT NUMBER 4

Description AE/ADR: .....

.....

.....

Start date: |___|___||___|___||___|___|___|___|

Ongoing ☐ Yes ☐ No If **NO**, indicate Stop date|___|___||___|___||___|___|___|___|

SERIOUSNESS				CORRALATION				EXPECTEDNESS			
Serious*	☐	**Not Serious**	☐	**Correlated**	☐	**Not correlated**	☐	**Expected**	☐	**Unexpected**	☐

**If Serious you must complete the SAE/SADR Reporting form and the relative CRF section*

ADVERSE EVENT NUMBER 5

Description AE/ADR: .....

.....

.....

Start date: |___|___||___|___||___|___|___|___|

Ongoing ☐ Yes ☐ No If **NO**, indicate Stop date|___|___||___|___||___|___|___|___|

SERIOUSNESS				CORRALATION				EXPECTEDNESS			
Serious*	☐	**Not Serious**	☐	**Correlated**	☐	**Not correlated**	☐	**Expected**	☐	**Unexpected**	☐

**If Serious you must complete the SAE/SADR Reporting form and the relative CRF section*

ADVERSE EVENT NUMBER 6

Description AE/ADR: .....

.....

.....

Start date: |___|___||___|___||___|___|___|___|

Ongoing ☐ Yes ☐ No If **NO**, indicate Stop date|___|___||___|___||___|___|___|___|

SERIOUSNESS				CORRALATION				EXPECTEDNESS			
Serious*	☐	**Not Serious**	☐	**Correlated**	☐	**Not correlated**	☐	**Expected**	☐	**Unexpected**	☐

**If Serious you must complete the SAE/SADR Reporting form and the relative CRF section*

ADVERSE EVENT NUMBER 7

Description AE/ADR: .....

.....

.....

Start date: |___|___||___|___||___|___|___|___|

Ongoing ☐ Yes ☐ No If **NO**, indicate Stop date|___|___||___|___||___|___|___|___|

SERIOUSNESS				CORRALATION				EXPECTEDNESS			
Serious*	☐	**Not Serious**	☐	**Correlated**	☐	**Not correlated**	☐	**Expected**	☐	**Unexpected**	☐

**If Serious you must complete the SAE/SADR Reporting form and the relative CRF section*

ADVERSE EVENT NUMBER 8

Description AE/ADR: .....

.....

.....

Start date: |___|___||___|___||___|___|___|___|

Ongoing ☐ Yes ☐ No If **NO**, indicate Stop date|___|___||___|___||___|___|___|___|

SERIOUSNESS				CORRALATION				EXPECTEDNESS			
Serious*	☐	**Not Serious**	☐	**Correlated**	☐	**Not correlated**	☐	**Expected**	☐	**Unexpected**	☐

**If Serious you must complete the SAE/SADR Reporting form and the relative CRF section*

ADVERSE EVENT NUMBER 9

Description AE/ADR: .....

.....

.....

Start date: |___|___||___|___||___|___|___|___|

Ongoing ☐ Yes ☐ No If **NO**, indicate Stop date|___|___||___|___||___|___|___|___|

SERIOUSNESS				CORRALATION				EXPECTEDNESS			
Serious*	☐	**Not Serious**	☐	**Correlated**	☐	**Not correlated**	☐	**Expected**	☐	**Unexpected**	☐

**If Serious you must complete the SAE/SADR Reporting form and the relative CRF section*

ADVERSE EVENT NUMBER 10

Description AE/ADR: .....

.....

.....

Start date: |___|___||___|___||___|___|___|___|

Ongoing ☐ Yes ☐ No If **NO**, indicate Stop date|___|___||___|___||___|___|___|___|

SERIOUSNESS				CORRALATION				EXPECTEDNESS			
Serious*	☐	**Not Serious**	☐	**Correlated**	☐	**Not correlated**	☐	**Expected**	☐	**Unexpected**	☐

**If Serious you must complete the SAE/SADR Reporting form and the relative CRF section*

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	**SAE/ADR Number 1**

1. SERIOUS ADVERSE EVENT NUMBER 1			
Diagnosis of SAE			
Details of the event:			
Onset date /____/____/____/ dd mm yy	End date /____/____/____/ dd mm yy		Ongoing ☐
Severity of event	Mild: ☐	Moderate: ☐	Severe: ☐
Expectedness	Expected: ☐	Unexpected: ☐	

***2.* SERIOUSNESS CRITERIA**			
Death ☐	Life threatening ☐	Persistent or significant disability/incapacity ☐	A congenital anomaly/birth defect ☐
Hospitalization or prolonged Hospitalization ☐ from /____/____/____/ to /____/____/____/ dd mm yy dd mm yy	Ongoing ☐	Medically significant ☐	

***3.* RELATIONSHIP TO STUDY INVESTIGATIONAL PRODUCT**					
Not related ☐	Unassessable ☐	Unlikely ☐	Possible ☐	Probable ☐	Certain ☐
Comments on Causality:					

***4.* OUTCOME OF ADVERSE EVENT**			
Not yet recovered ☐	Recovered without sequelae ☐		Recovered with sequelae ☐
Sequelae:			Unknown ☐
	Improved ☐		Worsened ☐
Fatal ☐	Date of death /____/____/____/ dd mm yy		Autopsy performed ☐
	Autopsy report attached ☐	Probable cause of death:	

5. STUDY INVESTIGATIONAL PRODUCT INFORMATION

Investigational Product	**Route**	**Batch N°**	**Expiry date** mm/yy	**Daily dose**	**Start date** dd/mm/yy	**Stop date** dd/mm/yy	**on-going**
					/____/____/____/	/____/____/____/	☐

6. ACTION TAKEN REGARDING STUDY DRUG			
None ☐	Reduced ☐	Temporarily interrupted ☐	Discontinued ☐
Specify dosage:	Interrupted from /____/____/____/ to /____/____/____/ dd mm yy dd mm yy		

Did event disappear after discontinuation?	Yes ☐	No ☐	NA ☐
Did event reappear after reintroduction?	Yes ☐	No ☐	NA ☐
Was the blind broken?	Yes ☐	No ☐	NA ☐

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	**SAE/ADR Number 2**

1. SERIOUS ADVERSE EVENT NUMBER 2			
Diagnosis of SAE			
Details of the event:			
Onset date /____/____/____/ dd mm yy	End date /____/____/____/ dd mm yy		Ongoing ☐
Severity of event	Mild: ☐	Moderate: ☐	Severe: ☐
Expectedness	Expected: ☐	Unexpected: ☐	

***2.* SERIOUSNESS CRITERIA**			
Death ☐	Life threatening ☐	Persistent or significant disability/incapacity ☐	A congenital anomaly/birth defect ☐
Hospitalization or prolonged Hospitalization ☐ from /____/____/____/ to /____/____/____/ dd mm yy dd mm yy	Ongoing ☐	Medically significant ☐	

***3.* RELATIONSHIP TO STUDY INVESTIGATIONAL PRODUCT**					
Not related ☐	Unassessable ☐	Unlikely ☐	Possible ☐	Probable ☐	Certain ☐
Comments on *Causality*:					

***4.* OUTCOME OF ADVERSE EVENT**		
Not yet recovered ☐	Recovered without sequelae ☐	Recovered with sequelae ☐
Sequelae:		Unknown ☐
	Improved ☐	Worsened ☐
Fatal ☐	Date of death /____/____/____/ dd mm yy	Autopsy performed ☐
	Autopsy report attached ☐	Probable cause of death:

5. STUDY INVESTIGATIONAL PRODUCT INFORMATION

Investigational Product	**Route**	**Batch N°**	**Expiry date** mm/yy	**Daily dose**	**Start date** dd/mm/yy	**Stop date** dd/mm/yy	**on-going**
					/____/____/____/	/____/____/____/	☐

6. ACTION TAKEN REGARDING STUDY DRUG			
None ☐	Reduced ☐	Temporarily interrupted ☐	Discontinued ☐
Specify dosage:	Interrupted from /____/____/____/ to /____/____/____/ dd mm yy dd mm yy		

Did event disappear after discontinuation?	Yes ☐	No ☐	NA ☐
Did event reappear after reintroduction?	Yes ☐	No ☐	NA ☐
Was the blind broken?	Yes ☐	No ☐	NA ☐

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	**SAE/ADR Number 3**

1. SERIOUS ADVERSE EVENT NUMBER 3			
Diagnosis of SAE			
Details of the event:			
Onset date /____/____/____/ dd mm yy	End date /____/____/____/ dd mm yy		Ongoing ☐
Severity of event	Mild: ☐	Moderate: ☐	Severe: ☐
Expectedness	Expected: ☐	Unexpected: ☐	

2. SERIOUSNESS CRITERIA			
Death ☐	Life threatening ☐	Persistent or significant disability/incapacity ☐	A congenital anomaly/birth defect ☐
Hospitalization or prolonged Hospitalization ☐ from /____/____/____/ to /____/____/____/ dd mm yy dd mm yy	Ongoing ☐	Medically significant ☐	

3. RELATIONSHIP TO STUDY INVESTIGATIONAL PRODUCT					
Not related ☐	Unassessable ☐	Unlikely ☐	Possible ☐	Probable ☐	Certain ☐
Comments on Causality:					

4. OUTCOME OF ADVERSE EVENT		
Not yet recovered ☐	Recovered without sequelae ☐	Recovered with sequelae ☐
Sequelae:		Unknown ☐
	Improved ☐	Worsened ☐
Fatal ☐	Date of death /____/____/____/ dd mm yy	Autopsy performed ☐
	Autopsy report attached ☐	Probable cause of death:

5. STUDY INVESTIGATIONAL PRODUCT INFORMATION

Investigational Product	**Route**	**Batch N°**	**Expiry date** mm/yy	**Daily dose**	**Start date** dd/mm/yy	**Stop date** dd/mm/yy	**on-going**
					/____/____/____/	/____/____/____/	☐

6. ACTION TAKEN REGARDING STUDY DRUG			
None ☐	Reduced ☐	Temporarily interrupted ☐	Discontinued ☐
Specify dosage:	Interrupted from /____/____/____/ dd mm yy to /____/____/____/ dd mm yy		

Did event disappear after discontinuation?	Yes ☐	No ☐	NA ☐
Did event reappear after reintroduction?	Yes ☐	No ☐	NA ☐
Was the blind broken?	Yes ☐	No ☐	NA ☐

SOMAGEL PROTOCOL **SUBJECT NUMBER** |___|___|___|	**SAE/ADR Number 4**

1. SERIOUS ADVERSE EVENT NUMBER 4			
Diagnosis of SAE			
Details of the event:			
Onset date /____/____/____/ dd mm yy	End date /____/____/____/ dd mm yy		Ongoing ☐
Severity of event	Mild: ☐	Moderate: ☐	Severe: ☐
Expectedness	Expected: ☐	Unexpected: ☐	

2. SERIOUSNESS CRITERIA			
Death ☐	Life threatening ☐	Persistent or significant disability/incapacity ☐	A congenital anomaly/birth defect ☐
Hospitalization or prolonged Hospitalization ☐ from /____/____/____/ to /____/____/____/ dd mm yy dd mm yy	Ongoing ☐	Medically significant ☐	

3. RELATIONSHIP TO STUDY INVESTIGATIONAL PRODUCT					
Not related ☐	Unassessable ☐	Unlikely ☐	Possible ☐	Probable ☐	Certain ☐
Comments on Causality:					

4. OUTCOME OF ADVERSE EVENT			
Not yet recovered ☐	Recovered without sequelae ☐		Recovered with sequelae ☐
Sequelae:			Unknown ☐
Improved ☐			Worsened ☐
Fatal ☐	Date of death /____/____/____/ dd mm yy		Autopsy performed ☐
	Autopsy report attached ☐	Probable cause of death:	

5. STUDY INVESTIGATIONAL PRODUCT INFORMATION

Investigational Product	**Route**	**Batch N°**	**Expiry date** mm/yy	**Daily dose**	**Start date** dd/mm/yy	**Stop date** dd/mm/yy	**on-going**
					/____/____/____/	/____/____/____/	☐

6. ACTION TAKEN REGARDING STUDY DRUG			
None ☐	Reduced ☐	Temporarily interrupted ☐	Discontinued ☐
Specify dosage:	Interrupted from /____/____/____/ to /____/____/____/ dd mm yy dd mm yy		

Did event disappear after discontinuation?	Yes ☐	No ☐	NA ☐
Did event reappear after reintroduction?	Yes ☐	No ☐	NA ☐
Was the blind broken?	Yes ☐	No ☐	NA ☐

INVESTIGATOR'S DECLARATION

I state that all data in this Case Report Form have been entered under my responsibility and to the best of my knowledge are accurate and complete, as required by the protocol.

Date |___|___||___|___||___|___|___|___|
dd/mm/yyyy

Investigator's Name: .....

Investigator's Signature: .....

16 APPENDICES

16.1 STUDY INFORMATION

16.1.3 List of IECs or IRBs

Appendix 16.1.3 List of IECs or IRBs

Table A. Independent Ethics Committee information.

Centre name	Clinical Pharmacology Centre for Drug Experimentation, University Hospital, Via Roma 67, I-56100 Pisa (Italy).
Investigator	Dr. Giovanni Gori
Ethics committee	Comitato Etico Regione Toscana Area Vasta Nord Ovest
Chairman	Romano Danesi
Date of approval of the final protocol	20th September 2018
Date of approval of amendment 1	NA
Date of approval of amendment 2	NA
Date of approval of amendment 3	NA

AZIENDA OSPEDALIERO-UNIVERSITARIA PISANA
D.A.I. DI AREA MEDICA E ONCOLOGIA
CENTRO DI FARMACOLOGIA CLINICA PER LA SPERIMENTAZIONE DEI FARMACI
DIRETTORE: PROF. CORRADO BLANDIZZI

Mod. C1

Vers_20160118

Gentile Sig.ra, le informazioni contenute nel seguente foglio informativo sono dettagliate e potrebbero risultare MOLTO COMPLESSE

Le chiediamo di accettare la partecipazione allo studio SOLO dopo avere letto con attenzione questo foglio informativo ed avere avuto un COLLOQUIO ESAURIENTE con il medico sperimentatore che le dovrà dedicare il TEMPO NECESSARIO per comprendere completamente ciò che le viene proposto

CLINICA MEDICA "G. MONASTERIO" - VIA ROMA, 67 - 56126 PISA
TELEFONO: 050-993954 FAX: 050-993431 E-MAIL: sperimentazionefarmaci@ao-pisa.toscana.it

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DIRETTORE PROF. CORRADO BLANDIZZI

Mod. C1.a

Vers_20160118

INFORMAZIONI SCRITTE PER IL PAZIENTE

Versione *2.0 del 17/07/2018*

Titolo dello studio:	Studio in aperto, su un gruppo di 30 donne sane per valutare la Biodisponibilità, la sicurezza e la tollerabilità locale della nuova formulazione in gel di Somatoline®
Codice Protocollo, versione e data:	Protocollo Somagel, versione 1.0 del 9 Luglio 2018
Eudract number:	2018-002380-26
Promotore dello studio:	Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni Via Baldanzese, 177, 50041 Calenzano – Firenze, Italia - Tel: (+39) 055 8835320
Sperimentatore Principale:	Dott. Giovanni Gori, Centro di farmacologia clinica per la sperimentazione dei farmaci, Azienda Ospedaliero-Universitaria Pisana indirizzo mail: giovannigori.gori@gmail.com, numero di telefono: (+39) 050993240

Gentile Sig.ra/ Sig.na,

Le è stato chiesto di partecipare ad uno studio clinico sperimentale e questo documento ha lo scopo di informarLa sulla natura dello studio, sul fine che esso si propone, su ciò che comporterà per Lei una tale partecipazione, sui suoi diritti e le sue responsabilità.

La prego di leggere attentamente queste informazioni scritte prima di prendere una decisione in merito ad una eventuale Sua partecipazione allo studio. Lei avrà a disposizione tutto il tempo necessario per decidere se partecipare o meno.

Potrà, inoltre, porre liberamente qualsiasi domanda di chiarimento e riproporre ogni quesito che non abbia ricevuto una risposta chiara ed esauriente.

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Nel caso in cui, dopo aver letto e compreso tutte le informazioni ivi fornite, decidesse di voler partecipare allo studio clinico, Le chiederò di voler firmare e personalmente datare il modulo di Consenso Informato allegato a questo documento.

Che cosa si propone lo studio

Lo studio prevede l'applicazione locale, nella zona delle cosce, della nuova formulazione in Gel di Somatoline® in donne sane. Ad oggi, Somatoline® è in commercio nella formulazione bustine di emulsione per uso cutaneo, come preparato farmaceutico indicato nel trattamento dell'adiposità cutanea localizzata accompagnata da cellulite.

La cellulite, o panniculopatia Edemato Fibro Sclerotica, è un'alterazione del tessuto cutaneo dovuta all'accumulo di liquidi e la sua comparsa è causata principalmente da un'alterazione del microcircolo con accumulo di liquidi nei tessuti cutanei.

I principi attivi presenti nella formulazione emulsione sono levo-tiroxina (0.1%) ed escina (0.3%). La levo-tiroxina è una molecola che attiva i processi di combustione negli adipociti e ne riduce le dimensioni, ostacola l'eccessiva produzione delle fibre di collagene che formano la "gabbia" che imprigiona le cellule adipose, causa della pelle a "buccia d'arancia". La molecola Escina è una saponina contenuta nei semi dell'ippocastano, che migliora il microcircolo riducendo l'accumulo di liquidi nei tessuti. Agisce sulle membrane dei capillari, migliorandone la resistenza.

La nuova formulazione in gel presenta gli stessi principi attivi nella stessa concentrazione dell'emulsione attualmente in commercio, quindi: Levo-tiroxina 0.1% ed Escina 0.3%.

L'obiettivo primario di questo studio è la valutazione della biodisponibilità sistemica della l-tiroxina libera (FT4).

L'obiettivo secondario dello studio è la valutazione della sicurezza del prodotto, analizzando la biodisponibilità sistemica di rT3, T3 e TSH, dopo ripetute applicazioni cutanee di una formulazione di gel di Somatoline®, e la tollerabilità locale e sistemica dopo ripetuta applicazione cutanea di una formulazione di gel di Somatoline®.

Per biodisponibilità si intende valutare la percentuale del principio attivo che raggiunge il flusso sanguigno, mentre la sicurezza del farmaco verrà monitorata tramite la concentrazione di TSH o *ormone tireotropo nel sangue dopo applicazione locale del gel Somatoline®.*

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Quali sono le caratteristiche di questo studio

Si tratta di uno studio condotto in aperto, ovvero sia Lei che il Suo medico sarete a conoscenza del trattamento. Verranno arruolate circa 30 donne volontarie sane in un singolo gruppo che verrà gestito presso un solo centro in Italia.

Cosa comporta la sua partecipazione allo studio

Prima di iniziare lo studio, Le verrà chiesto di leggere e firmare questo foglio informativo e consenso informato per il soggetto.

Se deciderà di partecipare allo studio, dovranno essere eseguite sei (6) visite totali presso il centro.

Il trattamento durerà complessivamente 28 giorni, di cui i primi due saranno di "attacco", cioè tratterà la zona delle cosce con una dose maggiore di Gel e successivamente di "mantenimento", trattando la zona con una dose ridotta. A questa fase seguirà un periodo di follow-up di 14 giorni, per una durata complessiva dello studio di 42 giorni per ogni soggetto.
Le verrà inoltre richiesto di compilare un Diario del soggetto per tutti i 28 giorni di trattamento.

Indagini a cui sarà sottoposta durante lo studio

Nella prima visita al centro, definita visita di Screening, saranno valutati i criteri di inclusione ed esclusione, i Suoi dati anagrafici e anamnestici (dati riguardanti la Sua storia clinica), e le terapie concomitanti prima dell'inizio dello studio. Sempre durante questa visita sarà effettuato un esame fisico, verranno misurati i parametri vitali (pressione, temperatura corporea, frequenza cardiaca e respiratoria), l'altezza e il peso e sarà eseguito un prelievo di sangue per valutare i parametri tiroidei che verranno analizzati dal laboratorio locale di questo Ospedale, verrà raccolto un campione di urine, e Le sarà effettuato il test di gravidanza.

Il volume totale di sangue che sarà prelevato per le procedure dell'intero periodo di studio sarà di circa 100 ml.

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DIRETTORE PROF. CORRADO BLANDIZZI

Dopo aver ricevuto i risultati dal laboratorio, il medico La contatterà per pianificare, il prima possibile, al massimo entro 15 giorni dalla visita di Screening, la successiva visita definita Visita Basale.

Durante la Visita Basale il Medico svolgerà le seguenti attività: revisione dei criteri di inclusione/esclusione, esame fisico, misurazione dei parametri vitali e test di gravidanza sulle urine.

Una volta verificati e soddisfatti tutti i criteri di inclusione/esclusione Le verrà consegnato il prodotto in studio da utilizzare a casa per 28 giorni a partire dal Giorno 0 (visita Basale); il medico dello studio Le mostrerà e spiegherà come applicare il gel nella zona delle cosce.

Il giorno 0, dopo la prima somministrazione, dovrà rimanere in osservazione presso il Centro per 5 ore. Alla fine della visita, Le verrà consegnato il "Diario per il soggetto" e il personale del centro La istruirà sulla compilazione dello stesso. In questo diario Le verrà richiesto di annotare eventi che riguardano la zona trattata ed eventuali eventi che riguardano il suo stato di salute che si possono verificare durante il periodo di partecipazione allo studio.

Il giorno successivo tornerà al centro per un prelievo di sangue che servirà a valutare la concentrazione degli ormoni tiroidei.

Dopo 14 e 28 giorni dall'inizio del trattamento Le verrà chiesto di tornare al centro per una visita di valutazione dei segni vitali e verrà effettuato un prelievo di sangue per valutare gli ormoni tiroidei.

Il giorno 42, cioè 14 giorni dopo la fine del trattamento, Le verrà chiesto di tornare al centro per una Visita Finale, chiamata visita di Follow-up, durante la quale sarà effettuato un esame fisico, verranno misurati i parametri vitali (pressione, temperatura corporea, frequenza cardiaca e respiratoria), sarà eseguito un prelievo di sangue per valutare i parametri tiroidei, e un esame dell'urina per la valutazione della loduria.

Quali sono i benefici che potrà ricevere partecipando allo studio

Poiché si tratta di uno studio su volontari sani, non affetti da alcuna malattia, non trarrà da questo studio alcun beneficio diretto sul Suo stato di salute. Tuttavia, le conoscenze che verranno acquisite anche grazie alla Sua partecipazione, saranno di utilità per acquisire rilevanti conoscenze per il

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DAI. DI AREA MEDICA E ONCOLOGIA
CENTRO DI FARMACOLOGIA CLINICA PER LA SPERIMENTAZIONE DEI FARMACI
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progresso della medicina.

Quali sono i rischi derivanti dalla partecipazione allo studio

La partecipazione a uno studio può comportare inconvenienti e rischi. In caso di domande in merito a uno dei possibili rischi, si rivolga ai medici dello studio.

Come tutti gli altri farmaci, il trattamento in studio potrebbe provocare alcuni effetti indesiderati: in questo studio non sono attesi effetti indesiderati gravi dovuti al prodotto, tuttavia sono possibili reazioni nel sito di trattamento, quali rossore, gonfiore o prurito o alterazioni della funzione tiroidea, che sarà monitorata mediante prelievo di sangue per l'analisi degli ormoni tiroidei. Per maggiori dettagli riguardo uno dei possibili effetti collaterali Le chiediamo di rivolgersi al Medico responsabile dello studio.

Nel caso in cui si verifichi uno degli eventi sopra riportati, o qualsiasi evento importante che riguardi la sua salute, la invitiamo a contattare immediatamente il Medico dello studio.

In caso insorga un problema medico conseguente alla somministrazione del prodotto allo studio, Le saranno comunque assicurate le cure più idonee.

Qualora durante lo studio, divengano disponibili dati che possano influenzare la Sua volontà di continuare lo studio, Lei sarà tempestivamente ed opportunamente informata e, se necessario, Le sarà richiesto di firmare un nuovo consenso informato a proseguire il trattamento in corso.

Il Promotore ha stipulato una copertura assicurativa con la Compagnia Allianz Global Corporate & Specialty SE (Polizza n° 30374204), per eventuali danni derivanti da questo studio in accordo alla vigente normativa. L' assicurazione vale per i risarcimenti fino a concorrenza di euro 5.000.000,00 per sinistro e garantisce la copertura dei danni da responsabilità civile derivante dalla sperimentazione stessa fino a 1.000.000,00 di euro per paziente, non copre il valore eccedente il massimale, ed è operante esclusivamente per i danni manifestati entro 24 mesi dalla conclusione della sperimentazione e per richieste di risarcimento presentate non oltre 36 mesi dalla conclusione della sperimentazione stessa.

Tuttavia la polizza assicurativa, che garantisce la copertura dei danni da responsabilità civile

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derivante dalla sperimentazione, non copre il valore eccedente il massimale ed è operante esclusivamente per i danni la cui richiesta di risarcimento sia stata presentata non oltre il periodo previsto in polizza. Tale limitazione non inficia comunque il suo diritto ad ottenere il risarcimento da parte del responsabile dell'eventuale danno.

Trattamenti incompatibili con la sperimentazione

Durante il periodo di screening Le sarà chiesto di evitare qualsiasi farmaco, incluse medicine da banco. Nei 6 mesi precedenti lo screening è vietato qualsiasi trattamento con farmaci antitiroidei o qualsiasi uso terapeutico di iodio o di medicinali contenenti iodio (ad es. amiodarone, Somatoline®); *è inoltre vietato qualsiasi test diagnostico che abbia portato all'utilizzo di traccianti,* agenti di contrasto contenenti isotopi di iodio o iodio.
Nelle 4 settimane prima dello screening non è consentito alcun cambiamento nella dieta di alimenti contenenti iodio (ad es. sale iodato) o uso di disinfettanti (ad es. betadine), detergenti o qualsiasi prodotto sistemico o topico contenente iodio, compresi i collutori (ad es. Iodosan), dentifricio iodurato, douches, soluzione di Lugol; nelle 4 settimane prima dello screening è vietato qualsiasi uso di integratori alimentari e medicine a base di erbe.
Durante il periodo dello studio è prevista una assunzione giornaliera di sale iodato minore a 1.100 µg / giorno.

Rischio di gravidanza

Se Lei è incinta o se sta allattando non potrà partecipare allo studio. Se è in età fertile dovrà sottoporsi a test di gravidanza sulle urine durante la visita di screening e alla visita basale (prima dell'inizio del trattamento). A meno che Lei non possa avere figli a causa di un intervento chirurgico o per altre ragioni mediche (se ha subito un intervento di legatura delle tube, o Le sono state rimosse le ovaie o l'utero, o è in post-menopausa), durante tutto il periodo dello studio, Lei e il suo compagno dovrete acconsentire ad utilizzare un metodo contraccettivo adeguato al fine di evitare una gravidanza. Nel caso in cui non siano già in corso metodi contraccettivi ormonali (come gli estroprogestinici) o metodi invasivi (come la spirale intrauterina), saranno richiesti i metodi di barriera (es. preservativo).
Se Lei dovesse iniziare una gravidanza nel corso dello studio, dovrà immediatamente informare il Medico responsabile dello studio, che valuterà la migliore terapia ai fini della tutela della salute Sua e del nascituro. Se ciò dovesse verificarsi, dovrà essere interrotta la Sua partecipazione allo studio. Il Medico responsabile dello studio seguirà Lei e il decorso della gravidanza fino al termine.

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Campioni Biologici

Per la Sua partecipazione allo studio Le è richiesto di effettuare un prelievo di sangue (circa 10 ml) e una raccolta di campione di urine alla visita di Screening e alla Visita di Fine Studio. I Suoi campioni saranno analizzati dal laboratorio locale della struttura a cui Lei afferisce.

Possibili alternative

Poiché si tratta di uno studio su volontari sani, non affetti da alcuna malattia, non si fa riferimento a terapie alternative.

Cosa succede se decide di non partecipare allo studio

La partecipazione allo studio è del tutto volontaria: se decide di partecipare, avrà il diritto di ritirarsi dallo studio in qualsiasi momento e senza l'obbligo di fornire spiegazioni, dandone tuttavia comunicazione al medico dello studio, il Dott. Giovanni Gori, telefono 050993240. In tal caso non saranno raccolti ulteriori dati che La riguardano e potrà chiedere la cancellazione di quelli già raccolti. Le Sue eventuali cure mediche attuali non saranno compromesse dalla Sua decisione ed i

medici continueranno a seguirLa con la dovuta attenzione.

D'altra parte, la Sua partecipazione allo studio potrà essere interrotta se si verificheranno effetti indesiderati.

Procedure previste alla fine dello studio

Non sono previste ulteriori trattamenti una volta terminato lo studio.

Consenso ad informare il proprio medico di medicina generale

Per la migliore tutela della Sua salute, Le verrà chiesto di informare il Suo medico di medicina generale in merito alla sperimentazione alla quale accetta di partecipare: il coinvolgimento del Suo medico di medicina generale, è infatti molto importante, al fine di evitarLe possibili danni derivanti *dalla interazione di eventuali farmaci da lei assunti o altri prodotti che potrebbero interagire in*

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maniera anche grave con i trattamenti previsti dallo studio.
Le viene consegnata una lettera destinata al Suo medico curante. La lettera contiene tutte le informazioni relative alla Sua partecipazione allo studio, in particolare l'indicazione degli effetti delle terapie che riceverà durante la sperimentazione, dei farmaci che non deve assumere e dei trattamenti medici ai quali non deve sottoporsi, in quanto incompatibili o sconsigliati.

La invitiamo, nel Suo interesse e a tutela della Sua salute, a:

1) consegnare la lettera al Suo medico curante;
2) informare i medici che La seguono nella sperimentazione di ogni farmaco o prodotto omeopatico o fitoterapico che intendesse assumere e di ogni trattamento medico al quale intendesse sottoporsi.

Qualora Lei omettesse di fornire tali indispensabili informazioni, né il Suo medico curante, né i medici che La seguono nella sperimentazione potranno essere considerati responsabili per i danni derivanti dalla incompatibilità tra la sperimentazione e ogni diverso trattamento medico.
La avvertiamo inoltre che tali danni potrebbero non essere coperti dall'assicurazione stipulata al momento della Sua partecipazione allo studio.

Informazioni circa i risultati dello studio

Se Lei lo richiederà, alla fine dello studio potranno esserLe comunicati i risultati generali dello studio ed in particolare quelli che La riguardano.

INFORMAZIONI IN MERITO AL TRATTAMENTO DEI DATI PERSONALI:

Titolari del trattamento e relative finalità

Il Centro di sperimentazione Azienda Ospedaliera Universitaria Pisana e la Società Italo Britannica L.Manetti - H.Roberts & C., che ha commissionato lo studio che Le è stato descritto, ciascuno per

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gli ambiti di propria competenza e in accordo alle responsabilità previste dalle norme della buona pratica, tratteranno i Suoi dati personali, in particolare quelli sulla salute e, soltanto nella misura in cui sono indispensabili in relazione all'obiettivo dello studio, altri dati relativi alla Sua origine, ai Suoi stili di vita e alla Sua vita sessuale (ecc.), esclusivamente in funzione della realizzazione dello studio e a fini di farmacovigilanza.

A tal fine i dati indicati saranno raccolti dal Centro di sperimentazione e trasmessi al Promotore dello studio e alle persone o società esterne che agiscono per loro conto. Un elenco aggiornato dei soggetti terzi a cui i dati vengono trasferiti è disponibile presso il Promotore, su richiesta.

Lei è libero di non fornire il consenso al trattamento dei dati relativi al suo stato di salute (anamnesi, stile di vita etc.), tuttavia il trattamento di tali dati è indispensabile allo svolgimento dello studio: il rifiuto di conferirli non Le consentirà di parteciparvi.

Base giuridica del trattamento

I dati personali che fornirà per le finalità sopra riportate verranno trattati esclusivamente sulla base del Suo espresso consenso, che potrà revocare in ogni momento. L'eventuale revoca avrà valore solo per il futuro, restando valido il trattamento eseguito fino a quel momento.

Natura dei dati

Il medico che La seguirà nello studio La identificherà con un codice: i dati che La riguardano raccolti nel corso dello studio, ad eccezione del Suo nominativo, saranno trasmessi al Promotore, registrati, elaborati e conservati, per 25 venticinque anni dalla conclusione dello studio, unitamente al codice assegnatole all'inizio dello studio. Soltanto il medico e i soggetti autorizzati potranno collegare questo codice al Suo nominativo.

Modalità del trattamento

I dati verranno trattati applicando al trattamento le misure adeguate di sicurezza ai sensi degli artt. 32 e seguenti del Regolamento UE 2016/679 e, ciò, sia sotto un profilo organizzativo sia sotto un profilo tecnologico.

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CENTRO DI FARMACOLOGIA CLINICA PER LA SPERIMENTAZIONE DEI FARMACI
DIRETTORE: PROF. CORRADO BLANDIZZI

I dati, trattati mediante strumenti anche elettronici, saranno diffusi solo in forma rigorosamente anonima, ad esempio attraverso pubblicazioni scientifiche, statistiche e convegni scientifici. La Sua partecipazione allo studio implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, il personale del Promotore o delle società esterne che eseguono per conto della prima il monitoraggio e la verifica dello studio, il Comitato etico e le autorità sanitarie italiane e straniere potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.

Esercizio dei diritti

Potrà esercitare i Suoi diritti previsti dal Regolamento UE 2016/679 (es. accedere ai Suoi dati personali, integrarli, aggiornarli, rettificarli, cancellarli, opporsi al loro trattamento per motivi legittimi, limitare l'elaborazione dei dati errati e richiedere una copia, al termine della sperimentazione, o trasferire i Suoi dati a terza parte) rivolgendosi direttamente al centro di sperimentazione (nome e cognome:_____; indirizzo:_____) o, per il suo tramite, al Promotore. Potrà interrompere in ogni momento e senza fornire alcuna giustificazione la Sua partecipazione allo studio. In tal caso, i campioni biologici a Lei correlati verranno distrutti. Non saranno inoltre raccolti ulteriori dati che La riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

Data Protection Officer

Il Promotore si avvale di un responsabile per la protezione dei dati personali, anche noto come Data Protection Officer "DPO": Dott. Giuseppe Casareto, Amministratore Delegato, il quale può essere contattato all'indirizzo e-mail gcasareto@boltongroup.it (tel.: +39 02 6775664).

Anche il Centro di sperimentazione si avvale di un DPO:

NOME _____ COGNOME_____

il quale può essere contattato all'indirizzo e-mail: _____

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Ulteriori informazioni

Non sono previsti costi aggiuntivi a Suo carico derivanti dalla partecipazione allo studio, in quanto tutti i costi sono rimborsati dallo sponsor che fornisce il supporto economico necessario. Per la sua partecipazione allo studio riceverà un rimborso pari a 300,00 (trecento, 00) euro.

Il protocollo dello studio che Le è stato proposto è stato approvato dal Comitato Etico per la sperimentazione clinica Area Vasta Nord Ovest in data 13 Settembre 2018. Il Comitato Etico ha verificato la conformità dello studio alle Norme di Buona Pratica Clinica della Unione Europea ed ai principi etici espressi nelle Dichiarazione di Helsinki.

Lei potrà segnalare qualsiasi fatto ritenga opportuno evidenziare, relativamente alla ricerca che La riguarda, al Comitato Etico e/o alla Direzione Sanitaria di questa struttura ospedaliera.

Dott./Prof.	(Cognome)	(Nome)
Telefono		
Email		

_____	__/__/____	_____	_____
Nome per esteso del medico che ha consegnato l'informativa	Data	Ora	Firma

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MODULO DI CONSENSO INFORMATO

Mod. C1.b

Versione *2.0 del 17/07/2018*

Vers_20160118

Titolo dello studio:	Studio in aperto, su un gruppo di 30 donne sane per valutare la Biodisponibilità, la sicurezza e la tollerabilità locale della nuova formulazione in gel di Somatoline®
Codice Protocollo, versione e data:	Protocollo Somagel, versione 1.0 del 9 Luglio 2018
Eudract number:	2018-002380-26
Promotore dello studio:	Società Italo Britannica L. Manetti - H. Roberts & C. per Azioni Via Baldanzese, 177, 50041 Calenzano – Firenze, Italia - Tel: (+39) 055 8835320
Sperimentatore Principale:	Dott. Giovanni Gori, Centro di farmacologia clinica per la sperimentazione dei farmaci, Azienda Ospedaliero-Universitaria Pisana indirizzo mail: giovannigori.gori@gmail.com, numero di telefono: 050993240

Io sottoscritto/a _____ nata _____ il ___/___/_____ residente a_____ provincia _____ via/piazza _____ Tel._____ domicilio (se diverso dalla residenza) _____

DICHIARO

- di aver ricevuto dal Dottor _____ esaurienti spiegazioni in merito alla richiesta di partecipazione alla ricerca in oggetto, secondo quanto riportato nella scheda informativa, facente parte di questo consenso, della quale mi è stata consegnata una copia in data _____ alle ore _____ (*indicare data e ora della consegna*);
- che mi sono stati chiaramente spiegati e di aver compreso la natura, le finalità, le procedure, i benefici attesi, i rischi e gli inconvenienti possibili e le alternative dello studio clinico;

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- di aver avuto l'opportunità di porre domande chiarificatrici e di aver avuto risposte soddisfacenti;
- di aver avuto tutto il tempo necessario prima di decidere se partecipare o meno;

- di non aver avuto alcuna coercizione indebita nella richiesta del Consenso;
- che mi è stato chiaramente spiegato di poter decidere liberamente di non prendere parte allo studio o di uscirne in qualsiasi momento senza fornire giustificazione, e che tali decisioni non modificheranno in alcun modo i rapporti con i medici curanti e con la struttura presso la quale sono in cura;
- Sono consapevole della necessità, diretta a garantire la migliore tutela della mia salute, di informare il mio medico curante della sperimentazione alla quale accetto di partecipare, consegnandogli la lettera a lui indirizzata; nel caso decida di non informarlo o ometta di farlo, né il mio medico curante né i medici che mi seguono nella sperimentazione saranno considerati responsabili per i danni che possano derivare dall'incompatibilità tra la sperimentazione e qualunque altro diverso trattamento medico o farmaco o prodotto omeopatico o fitoterapico io abbia assunto. Inoltre sono consapevole che tali danni potrebbero non essere coperti dall'assicurazione stipulata al momento della mia decisione di partecipare allo studio.
- Sono consapevole che una mia gravidanza è incompatibile con la sperimentazione e mi impegno ad evitarla adottando le misure di prevenzione della gravidanza previste nel protocollo e descritte dettagliatamente nel testo informativo.

DICHIARO pertanto di

☐ **volere** ☐ **NON volere**
partecipare allo studio

☐ **volere** ☐ **NON volere**
essere informato sui risultati di questa ricerca dal medico dello studio

☐ **volere** ☐ **NON volere**
essere informato sui risultati della ricerca dal medico dello studio, anche in relazione alle notizie inattese che dovessero essere accidentalmente riscontrate con le indagini previste dallo studio

☐ **volere** ☐ **NON volere**

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Informare il medico di medicina generale della partecipazione allo studio

☐ **accettare** ☐ **NON accettare**
alla raccolta dei campioni biologici (sangue e urina) previsti dallo studio.
(*Nota: la scelta "Non acconsento" non permette di partecipare allo studio*).

☐ **accettare** ☐ **NON accettare**
Di segnalare una mia eventuale gravidanza, che dovesse verificarsi nonostante la contraccezione richiesta dal protocollo, e autorizzo la raccolta dei dati relativi alla gravidanza da parte del Medico sperimentatore.

_____	__/__/____	_____	_____
Nome per esteso del paziente	Data	Ora	Firma

_____	__/__/____	_____	_____
Nome per esteso testimone imparziale* (ove applicabile)	Data	Ora	Firma

*Il testimone imparziale è una persona che sia indipendente dallo studio, che non possa essere influenzata in alcun modo dalle persone coinvolte nello studio, che partecipi alla procedura di informazione del paziente se il paziente non è in condizione di leggere e che legga il consenso informato e ogni altra informazione scritta fornita al paziente partecipante.

Sottoscrivendo questo modulo acconsento al trattamento dei miei dati personali e al loro trasferimento al di fuori dell'Unione europea per gli scopi della ricerca nei limiti e con le modalità indicate nell'informativa fornitami con il presente documento.

_____	__/__/____	_____	_____
Nome per esteso del paziente	Data	Ora	Firma

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AZIENDA OSPEDALIERO-UNIVERSITARIA PISANA
D.A.I. DI AREA MEDICA E ONCOLOGIA
CENTRO DI FARMACOLOGIA CLINICA PER LA SPERIMENTAZIONE DEI FARMACI
DIRETTORE: PROF. CORRADO BLANDIZZI

_____	__/__/____	_____	_____
Nome per esteso testimone imparziale (ove applicabile)	Data	Ora	Firma

lo sottoscritto Prof./Dr.

....
Cognome Nome

Dichiaro che il Volontario ha firmato spontaneamente la sua partecipazione allo studio

Dichiaro inoltre di:

- aver fornito al Volontario esaurienti spiegazioni in merito alle finalità dello studio, alle procedure, ai possibili rischi e benefici e alle sue possibili alternative;
- aver verificato che il Volontario abbia sufficientemente compreso le informazioni fornitegli
- aver lasciato al Volontario il tempo necessario e la possibilità di fare domande in merito allo studio
- non aver esercitato alcuna coercizione od influenza indebita nella richiesta del Consenso

_____	__/__/____	_____	_____
Nome per esteso del medico che ha fornito le informazioni e *raccolto il consenso informato*	Data	Ora	Firma

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NOTA BENE

una copia del presente modulo, firmato e datato, allegato alle "Informazioni scritte per il Volontario" dovrà essere consegnata al Paziente stesso

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16 APPENDICES

16.1 STUDY INFORMATION

16.1.4 List and description of investigators and other important participants in the study

16.1.4 List and description of investigators and other important participants in the study

Title	Name and affiliation
Principal Investigator	Dr. Giovanni Gori, Clinical Pharmacology Centre for Drug Experimentation, University Hospital, Via Roma 67, I-56100 Pisa (Italy).
Sponsor	L. Manetti - H. Roberts & C. per Azioni, Via Baldanzese, 177, 50041 - Calenzano – (FI), Italy
Project Managers	Dr. Elisabetta Di Martino, Pharmaceutical Development and Services srl, via dei Pratoni 16, I-50018 Scandicci (Firenze, Italy). Dr. Luisa Di Cerbo, Pharmaceutical Development and Services srl, via dei Pratoni 16, I-50018 Scandicci (Firenze, Italy).
Project Leaders	Dr. Cristina Sabatini, L. Manetti - H. Roberts & C. per Azioni, Via Baldanzese, 177, 50041 - Calenzano – (FI), Italy. Dr. Barbara Tracuzzi, L. Manetti - H. Roberts & C. per Azioni, Via Baldanzese, 177, 50041 - Calenzano – (FI), Italy.
Clinical Research Assocate	Dr. Luisa Di Cerbo, Pharmaceutical Development and Services srl, via dei Pratoni 16, I-50018 Scandicci (Firenze, Italy).
Data Management	Dr. Flavio Mascagni, Pharmaceutical Development and Services srl, Via dei Pratoni 16, I-50018 Scandicci (Firenze, Italy).

16 APPENDICES

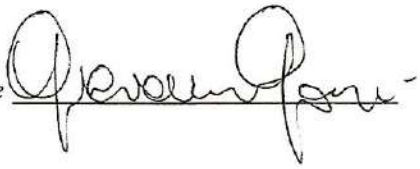
16.1 STUDY INFORMATION

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer

PROTOCOL VERIFICATION

PRINCIPAL INVESTIGATOR
Name, Surname: Giovanni Gori
Address: Clinical Pharmacology Centre for Drug Experimentation, University Hospital

I have read this protocol and agree to conduct this trial in accordance with all the stipulations of the protocol and in accordance with the Declaration of Helsinki.

Signature  *Date* 11/JUL/2018

16 APPENDICES

APPENDIX 16.1 STUDY INFORMATION

Appendix 16.1.6 Listing of patients receiving test drug(s)investigational product(s) from specific batches

Appendix 16.1.6 Listing of patients receiving test drug(s)investigational product(s) from specific batches

Screening Number	Sex	IC signature Date	Enrollment Y/N	Enrollment Date
01-001	F	21/01/2019	Y	28/01/2019
01-002	F	21/01/2019	Y	28/01/2019
01-005	F	31/01/2019	Y	04/03/2019
01-007	F	01/02/2019	Y	04/03/2019
01-012	F	06/02/2019	Y	04/03/2019
01-017	F	08/02/2019	Y	04/03/2019
01-006	F	31/01/2019	Y	05/03/2019
01-003	F	31/01/2019	Y	06/03/2019
01-010	F	06/02/2019	Y	06/03/2019
01-011	F	06/02/2019	Y	06/03/2019
01-016	F	08/02/2019	Y	06/03/2019
01-009	F	01/02/2019	Y	12/03/2019
01-013	F	06/02/2019	Y	12/03/2019
01-019	F	05/03/2019	Y	12/03/2019
01-023	F	08/03/2019	Y	18/03/2019
01-024	F	11/03/2019	Y	18/03/2019
01-025	F	11/03/2019	Y	18/03/2019
01-021	F	08/03/2019	Y	19/03/2019
01-022	F	08/03/2019	Y	21/03/2019
01-026	F	12/03/2019	Y	21/03/2019
01-028	F	14/03/2019	Y	21/03/2019
01-029	F	15/03/2019	Y	21/03/2019
01-018	F	05/03/2019	Y	25/03/2019
01-020	F	05/03/2019	Y	25/03/2019
01-030	F	20/03/2019	Y	25/03/2019
01-031	F	20/03/2019	Y	25/03/2019
01-032	F	21/03/2019	Y	26/03/2019
01-033	F	22/03/2019	Y	26/03/2019
01-027	F	14/03/2019	Y	26/03/2019
01-034	F	27/03/2019	Y	02/04/2019
01-004	F	31/01/2019	N	(Screeining Failure)
01-008	F	01/02/2019	N	(Consent withdrawal)
01-014	F	08/02/2019	N	(Consent withdrawal)
01-015	F	08/02/2019	N	(Consent withdrawal)

16 APPENDICES

16.1 STUDY INFORMATION

16.1.7 Randomization scheme and codes

NA

16 APPENDICES

16.1 STUDY INFORMATION

16.1.8 Audit certificates

NA

16 APPENDICES

16.1 STUDY INFORMATION

16.1.9 Documentation of statistical methods

Statistical Analysis Plan

Somagel

EudraCT number: 2018-002380-26

Single-group, open study on the systemic bioavailability, safety and local tolerability of a new gel formulation of Somatoline® in 30 healthy women.

Final Version 1.0

12th September 2018

SIGNATURE PAGE

I have read this analysis plan and confirm that to the best of my knowledge it accurately describes the planned statistical analyses of the study

Signature	Date
	12/09/2018

Cristina Sabatini
Regulatory Affairs Manager, Manetti & Roberts

	12/09/2018

Barbara Tracuzzi
Responsabile scientifico, Manetti & Roberts

	13/09/2018

FLAVIO MASCAGNI
STATISTICO, PHARMA D&S

1 Table Of Contents

1 TABLE OF CONTENTS 3

2 GLOSSARY 6

3 INTRODUCTION 8

3.1 Preface 8

3.2 Purpose of the analyses 8

4 STUDY OBJECTIVES AND ENDPOINTS 8

4.1 Study objectives 8

4.1.1 Primary objective(s) 8

4.1.2 Secondary objective(s) 8

4.2 End point(s) 9

5 STUDY METHODS 9

5.1 General Study Design and Plan 9

5.2 Inclusion-Exclusion Criteria and General Study Population 11

5.3 Randomization and treatment allocation 13

5.4 Study Variables 13

5.5 Derived variables 14

6 SAMPLE SIZE 15

7 GENERAL CONSIDERATIONS 15

7.1 Timing of analysis 15

7.2 Analysis populations 15

7.3 Covariates and Subgroups 16

7.4 Drop-outs, missing data and outliers 16

7.5 Interim analysis 16

8 STATISTICAL ISSUE 16

8.1 General methodology 16

8.2 Subject disposition 16

8.3 Protocol deviations 17

8.4 Baseline characteristics 17

8.5 Current illness and medical conditions 18

8.6 Prior and current medications 18

8.7 Treatment compliance 18

9 EFFICACY ANALYSES 18

9.1 Primary efficacy analysis 19

9.2 Secondary efficacy analyses 19

9.3 Safety efficacy analysis: 19

9.3.1 (Serious) Adverse events 19

9.3.2 Local tolerability assessment 20

9.3.3 Physical examination 20

9.3.4 Vital signs 20

9.3.5 ECGs 21

9.3.6 Clinical laboratory assays 21

10 SUMMARY OF CHANGES TO THE PROTOCOL 22

11 GENERAL DEFINITIONS 22

11.1 Computer systems and software to be used in the analysis 22

11.1 Reporting conventions 22

11.2 Coding systems used 23

11.2.1 Clinical Terms 23

11.2.2 *Drugs* 23

11.3 Report type, language and format 23

12 TABLE AND FIGURES 23

12.1 Statistical analysis report 23

12.2 Tables, headings and footnotes 23

12.3 List of Tables 24

12.4 Subject data listing 25

12.5 Figure 28

13 REFERENCES 28

2 Glossary

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
CR	Clinically Relevant
CV	Coefficient of Variability
DBP	Diastolic Blood Pressure
DoB	Date of Birth
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoS	End of Study
EoT	End of Treatment
fT_4	Free Thyroxine
GGT/γGT	Gamma-glutamyl transferase
Hcb	Hemoglobin
Hct	Hematocrit
HBs Ag	Hepatitis B virus surface antigen
HCV Ab	Hepatitis C virus antibodies
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IU	International Unit
ITT	Intention To Treat
$l\text{-}T_4$	Levothyroxine
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration

MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
NCR	Not Clinically Relevant
OTC	Over-the-counter
PI	Principal Investigator
PLT	Platelets
PP	Per Protocol
RF	Respiratory Frequency
RBC	Red Blood Cells
rT_3	Reverse Triiodothyronine
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOP	Standard Operating Procedure
SUSAR	Suspected, Unexpected Serious Adverse Drug Reaction
T_3	Triiodothyronine
T_4	Thyroxine
Temp	Body Temperature
TSH	Thyroid Stimulating Hormone
USDA	United States Dietary Allowance
WBC	White Blood Cells

3 Introduction

3.1 Preface

Aim of the study is to assess systemic bioavailability of l-T4 (safety and local tolerability) of a new gel formulation of Somatoline ® in 30 healthy women based on changes in bioavailability of FT4, FT3, rT3, and TSH.

3.2 Purpose of the analyses

Analyses described in this document will assess the bioavailability and safety of Somatoline ® and will be included in the Study Report.

4 Study Objectives and Endpoints

4.1 Study objectives

4.1.1 Primary objective(s)

The primary objective of the study is to assess the systemic bioavailability of l-T4 in female subjects with local cellulitis after repeated cutaneous of a gel formulation of Somatoline® according to the proposed posology as per Investigator's Brochure.

4.1.2 Secondary objective(s)

The secondary objectives of the study are:

- to assess the systemic bioavailability of T4, rT3, and TSH, after repeated cutaneous application of a gel formulation of Somatoline® in female subjects with local cellulitis;
- to assess the local and systemic tolerability after repeated cutaneous application of a gel formulation of Somatoline® in female subjects with local cellulitis.

4.2 End point(s)

The primary end-point is the comparison of the pre-treatment plasma concentrations of l-T_4 with those observed 24 hours, 14 days and 28 days after a cutaneous repeated application of Somatoline® gel, and 14 days after the last application of the gel (Day 42 of follow-up).

The secondary end-point is the comparison of the plasma concentrations of T_3, rT_3, and TSH with those observed 24 hours, 14 days and 28 days after a cutaneous repeated application of Somatoline® gel, and 14 days after the last application of the gel (Day 42 of follow-up).

5 Study Methods

5.1 General Study Design and Plan

The study will be run according to a single-group, open design.

Briefly, a group of 30 Caucasian healthy woman, aged between 18 and 50 years, will be selected for the participation into the study, during a Screening period which cannot last more than 15 days (Day -15 to Day 0).

Women will be early informed about the purposes of the study and the risks related to the study participation. If they agree to participate, they will be consented with the most recently approved Informed Consent Form (ICF), and then evaluated for their compliance to the inclusion and exclusion criteria. Once the eligibility of women has been confirmed, they will be assessed for plasma concentrations of T4, T3, rT3 and TSH.

No dietary changes of iodine-containing food or changes in the use of iodine-containing disinfectants, detergents or mouthwash products will be allowed during the study. A maximal daily intake of iodized salt of 1,100 µg/day is allowed. In order to check the compliance of the subjects with this requirement, the concentrations of iodide in the urine will be assessed at the Screening and End of Study (EOS).

At Baseline (Day 0), after a medical visit has reconfirmed the eligibility criteria and a negative pregnancy test has been obtained, the women will be assessed again for plasma concentrations of T4, T3, rT3 and TSH.

After these examinations, women will be instructed to apply Somatoline® 10 g gel (l-T4 10 mg/escin 30 mg) on each thigh per day during the first 2 days (20 grams per day in total), followed by 5 grams per thigh (10 grams per day in total) until the end of a 4-week period starting from the day the first

dose was applied. The subjects have to apply the product and then massage the skin of the entire thigh for several minutes until completely absorbed.

Blood samples for measurement of free T4, r-T3, and T3 and TSH levels will be repeated at Control 1 (Day 0, 5 hours after the first application of Somatoline®) and Control 2 (Day 1, 24 hours after the first application of Somatoline®), and then again on Day 14 and Day 28 (End of Treatment [EOT]).

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory frequency and body temperature) will be assessed at each visit. A full medical examination will be repeated at the EOS.

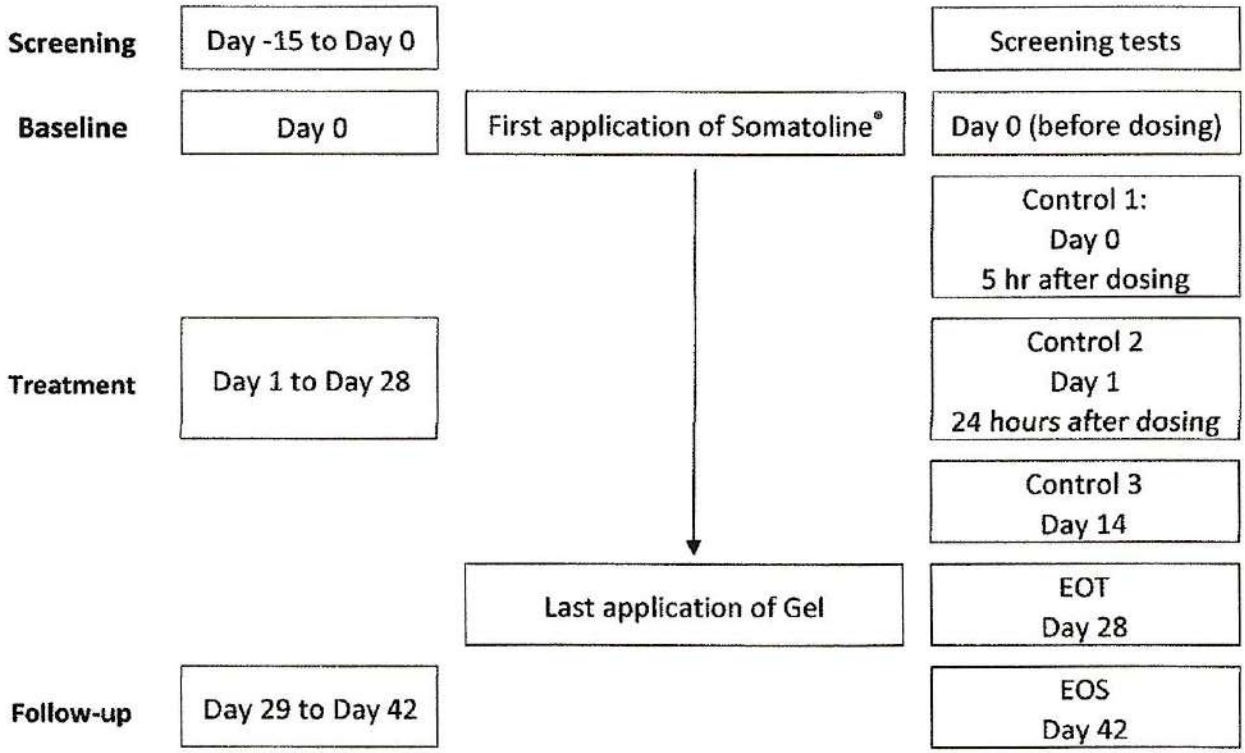
In order to assess the systemic tolerability of the treatment with Somatoline® gel, on Day 0, Day 1, Day 14 and Day 28, EOT and EOS (Follow-up), women will be asked for any adverse event (AE) or any issue observed during the treatment, and the bilateral sites of drug application will be inspected for any local reaction (erythema, swelling and itching), which will be scored. Moreover, a diary will be given to the patients at Day 0 and the patients will be asked to daily score any sign of erythema, swelling and itching, at the application site.

Finally, a 12-lead ECG will be run at the Screening and repeated on Day 0 (5 hours after the first Somatoline® application), on EOT and EOS, to assess any potential systemic absorption of T4 and related effects on cardiac activity.

After the EOT (Day 28), women will be followed for additional 14 days. During the follow-up period, no treatment with Somatoline® will be allowed.

On Day 42 (EOS), blood samples for measurement of free T4, r-T3, T3 and TSH levels will be drawn. On the same Day, women will be asked for any AE or any issue observed during the treatment, and the bilateral sites of drug application will be inspected for any local reaction, which will be scored.

STUDY FLOW CHART



5.2 Inclusion-Exclusion Criteria and General Study Population

Inclusion criteria: healthy woman will be enrolled in the study if they meet all the following inclusion criteria:

1. Sex and age: Adult women aged between 18 and 50 years;
2. Race: Caucasian;
3. Body mass index (BMI): 18.5 > BMI < 30 kg/m2;
4. Vital signs: systolic blood pressure (SBP) = 100-139 mmHg; diastolic blood pressure (DBP) = 50-89 mmHg; heart rate (HR) = 50-90 bpm, measured after 5 min of rest (sitting position);
5. Electrocardiogram (ECG): no clinically relevant abnormalities at ECG (12 leads);
6. Physical examination: no clinically relevant abnormal physical findings;
7. Laboratory analyses: no clinically relevant abnormal laboratory values indicative of physical illness;
8. Allergy: no ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients or ß lactam antibiotics;

9. Medical history: no history of anaphylaxis to drugs or allergic reactions in general, no relevant history of renal, hepatic, cardiovascular, respiratory, skin, haematological, endocrine, or neurological diseases that may interfere with the aim of the study, no history of gastric mucosal damages, no neoplasia, no medications during 2 weeks before the start of the study, including OTC ("over the counter");
10. Participation in another experimental trial: no participation in the evaluation of any experimental drug within 3 months prior to screening;
11. Blood donors: no blood donations during 3 months prior to this study;
12. Drug or alcohol history: no history of drug, alcohol (< 1 drink/day for females, defined according to USDA Dietary Guidelines 2000) or tobacco abuse (< 10 cigarettes/day);
13. Pregnancy: not pregnant or lactating (for female healthy subjects);
14. Contraception: fertile women willing to use barrier contraceptive methods;
15. Subjects' capability: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study;
16. ICF: signed written ICF prior to inclusion in the study;
17. Life-style: Willingness of the subject to maintain a constant life style during the period of the study.

Exclusion criteria: Women will be excluded from the study if they meet anyone of the following inclusion criteria:

1. Pregnancy: pregnant or lactating women;
2. ECG: clinically relevant abnormalities;
3. Physical findings: clinically relevant abnormal physical findings which could interfere with the study objectives;
4. Laboratory analyses: clinically relevant abnormal laboratory values indicative of physical illness;
5. Allergy: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considered to potentially affect the outcome of the study;
6. Diseases: relevant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine (in particular, thyroid), or neurological diseases, which may interfere with the aim of the study, history of gastric mucosal damages, neoplasia;
7. Contraceptive: changes (early or suspension) of the use of contraceptive oestrogen-progestin in the last 4 weeks, and inability to take adequate contraception during the study;

8. Medications and diet: any medication, including OTC, is forbidden during the screening period. Moreover:
    a. In the 6 months before screening, any treatment with antithyroid drugs or any therapeutic use of iodine or iodine-containing medications (e.g., amiodarone, Somatoline®) is forbidden;
    b. In the 6 months before screening, any diagnostic tests that led to the use of tracers, contrast agents containing iodine or iodine isotopes, is forbidden;
    c. in the 4 weeks before screening, no changes in diet of foods containing iodine (e.g., iodized salt), or use disinfectants (e.g., betadine), detergents or any systemic or topical product containing iodine, including mouthwashes (e.g., Iodosan), toothpaste iodinated, douches, Lugol's solution;
    d. In the 4 weeks before screening, any use of food supplements and herbal medicines;
    e. a daily intake of iodized salt < 1,100 µg/day.
9. Investigative drug trials: participation in the evaluation of any experimental drug within 3 months prior to the start of the study;
10. Blood donation: blood donations during the 3 months prior to this study;
11. Drug, alcohol, tobacco: history of drug, alcohol [> 1 drink/day for females defined according to USDA Dietary Guidelines 2000] or tobacco abuse (> 10 cigarettes/day).

5.3 Randomization and treatment allocation

The study is open with a single-group and there will be no randomization procedure.

5.4 Study Variables

The following table (Table 1) shows all the data that will be collected during the study, visit by visit. All analysis are better described in sections 8 and 9.

Table 1. Overall study schedule

Timing of event		Screening	Baseline (before dosing)	Control 1 Day 0	Control 2 Day 1	Control 3 Day 14	End of Treatment	End of Study (Follow-up)
		Day -15 to Day 0	Day 0	5 hours	24 hours	Day 14 +1	Day 28 +3	Day 42
Informed Consent		x						
Eligibility		x	x					
Demography & Lifestyle		x						
Medical History		x						
Hematology		x						x
Blood chemistry		x						x
Urine Drug Screening		x						
Urinalysis		x						x
Ioduria		x						x
Virology		x						
Alcohol/Nicotine Consumption		x						
TSH concentration[1]		x	x	x	x	x	x	x
Free T4, r-T3, T3[1]			x	x	x	x	x	x
Pregnancy Test		x	x					
Treatment[2]			x		x	x	x	x
Vital Sign (SBP, DBP, HR, RF, Temp)		x	x	x	x	x	x	x
Physical Examination		x	x					x
ECG		x						x
Adverse Events			x	x	x	x	x	x
Local Tolerability assessed	by investigators			x	x	x	x	x
	by subject (diary)			x	x	x	x	x

X[1]: Free T4, r-T3, T3 and TSH concentrations will be evaluated at Baseline before dosing and 5 hours after dosing, at Day 1 (24 hours after dosing) , at Day 14, at Day 28 and Day 42

X[2]: the treatment will start after the eligibility criteria reconfirmed, a negative pregnancy test and plasma concentrations obtained. The treatment starts on each thigh (10 grams) per day during the first two days, followed by 5 grams per thigh until the end of a 4-week period.

5.5 Derived variables

Age will be calculated as the difference between the baseline date (Day0) and date of birth (DoB).

SAS code: *age=FLOOR((INTCK('month',DoB,Day0)-day(Day0)<day(DoB)))/12);*

6 Sample size

Based on a prior experience conducted with a similar formulation (Certan et al. 2013) mean value of FT4 was assumed to be 11.0 ± 1.2 pg/mL and a sample size of 26 subjects was estimated to allow confirming the stability of said value during the study within confidence interval of ±0.7 (99% confidence interval). Assuming a dropout rate of 15% the decision was taken to enroll 30 subjects.

7 General Considerations

7.1 Timing of analysis

The final analysis will be performed after data base lock on data transferred from SAS-Pheedlt (eCRF) and after the finalization and approval of this SAP document.

7.2 Analysis populations

Three populations will be defined for use in the descriptive and inferential statistical analyses: the *Safety Population, the ITT Population and the PP Population.*

1. "INTENTION TO TREAT" (ITT population): All subjects who received the study drug and who participated in at least one post-baseline assessment.
2. "PER PROTOCOL" (PP Population): all subjects who concluded the study without important protocol deviations or violations.
3. "SAFETY" (Safety Population): all subjects who will be received at least one dose of the study drug.

Screened subjects (n=...)	→	Screening failures (n=...)
↓		
Subjects who received at least one dose of the study drug (n=...)	→	SAFETY POPULATION
↓		
Subjects who received the study drug and who participated in Control 1 (n=...)	→	ITT POPULATION
↓	→	Drop-outs (n=...) Major protocol deviations (n=...)
Subjects who completed the study without major protocol deviations (n=...)	→	PP POPULATION

7.3 Covariates and Subgroups

There will be no covariate or subgroups.

7.4 Drop-outs, missing data and outliers

Data not available will be assessed as "missing values", therefore no imputation methods or replacement will be applied for drop-out, missing or outliers.

7.5 Interim analysis

There will be no interim analysis.

8 Statistical issue

8.1 General methodology

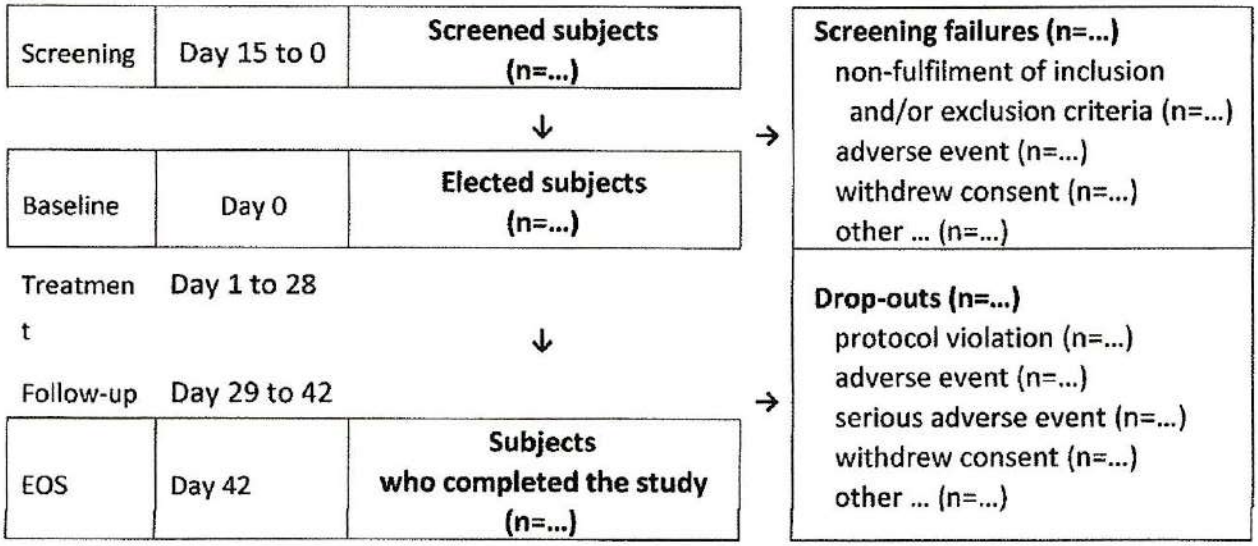
All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted when appropriate by visit number, with the total population size relevant to that table, including any missing observations.

8.2 Subject disposition

Variables from the CRF sections "Investigator confirmation of eligibility", "Screening failure" and "Treatment administration" will be used to establish how many screened subjects reached the treatment administration stage, how many screening failures and for what reasons (non-fulfilment of inclusion and/or exclusion criteria, adverse event, withdrew consent or other).

Variables from the CRF section "Subject's completion of the study or premature discontinuation" will be used to establish how many treated subjects completed the study, how many dropped out and for what reasons (protocol violation, adverse event, SAE, withdrew consent or other).

A skeleton diagram or a table will be provided in this section that provides the number of subjects screened, screening failure, treated, dropped out or completed.



8.3 *Protocol deviations*

Any change, divergence, or departure from the study design or procedures of a research protocol that affects the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data constitutes a **major protocol deviations/protocol violations.**

Changes or alterations in the conduct of the trial which do not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data are considered **minor protocol deviations**.

A data review will take place in order to discuss remaining issues (outstanding queries, unresolved errors), discuss the cases of major and minor protocol violations and determine on a case-by-case basis the subjects to be excluded from the PP population.

All protocol deviations will be listed indicating subject identification, reason and classification in minor or major deviation.

8.4 *Baseline characteristics*

Only healthy Caucasian women aged between 18 and 50 years will be enrolled in the study.

Quantitative data (age, height, weight, BMI) will be summarized using quantitative descriptive statistics such as mean, standard deviation, median, minimum and maximum values.

8.5 *Current illness and medical conditions*

AEs, medical history and concomitant diseases will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Version of coding dictionaries will be stated in the Study Report.

All data will be listed by subject and summarized by SOC and PT MedDRA® term.

8.6 *Prior and current medications*

Concomitant medications will not allowed at screening.

The complete list of concomitant medications will be displayed by subject, indicating in addition to route, dose, indication, start and end date (or ongoing), even if due to AE, SAE or medical history.

No dietary changes of iodine-containing food or changes in the use of iodine-containing disinfectants, detergents or mouthwash products will be allowed during the study. A maximum daily intake of iodized salt < 1,100 µg/day is allowed during the study.

In order to check the compliance of the subjects with this requirement, the concentrations of iodide in the urine will be assessed at the Screening and End of Study (EOS).

8.7 *Treatment compliance*

The subjects will be asked to complete a diary daily and to return the complete diary at the EOT. In this diary the subjects will declare if they have applied the IMP (Somatoline® gel) on the cutaneous surface of the right and left thighs.

A frequency table will indicate the percentage of treated thighs by zone and by day.

9 Efficacy analyses

All efficacy variables will be listed by subject.

All continuous efficacy variables will be summarized by visit with N, Mean, Standard Deviation, Minimum and Maximum and will be analyzed with analysis of variance with visits.

All plasma concentrations encoded by Investigators (Normal, Abnormal NCR and Abnormal CR) will be evaluated by frequency tables.

9.1 Primary efficacy analysis

Plasma concentrations of Free T_4 ng/dL (continuous variable) will be assayed at the following time points:

- Day 0 (pre-treatment), day 0 (5h), day 1 (24h), day 14, day 28 and day 42.

The comparison of the means from baseline will be performed with ANOVA.

9.2 Secondary efficacy analyses

Plasma concentrations of rT3 (continuous variable) will be assayed at the following time points:

- Day 0 (pre-treatment), day 0 (5h), day 1 (24h), day 14, day 28 and day 42.

Plasma concentrations of T3 µg/L (continuous variable) will be assayed at the following time points:

- Day 0 (pre-treatment), day 0 (5h), day 1 (24h), day 14, day 28 and day 42.

Plasma concentrations of TSH mUI/L (continuous variable) will be assayed at the following time points:

- Day -15/0 (screening), day 0 (pre-treatment), day 0 (5h), day 1 (24h), day 14, day 28 and day 42.

The comparison of the means from baseline will be performed with ANOVA.

9.3 Safety efficacy analysis:

9.3.1 (Serious) Adverse events

AEs/SAEs will be recorded throughout the entire study duration.

The incidence of AEs/SAEs will be evaluated by frequency tables providing, for each cross-classification and subcategory, the following frequencies:

- Total number of AEs/SAEs observed.
- Number and percentage of subjects reporting at least one AE/SAE.

When calculating the incidence of AE, or any sub-classification thereof by time period, severity, etc., each subject will only be counted once and any repetitions of adverse events will be ignored; the denominator will be the total population size.

9.3.2 *Local tolerability assessment*

Local tolerability of Somatoline® will be assessed by the Investigator and the subjects throughout the collection of data in the subject diary during the entire study duration.

The Investigator will assess the local tolerability at the application site (both sides, left and right) on Day 0 after 5 hours after the first application, Day 1, Day 14, Day 28 and Day 42, by scoring (0-3) each of the following parameters (Table 2):

- Redness;
- Swelling;
- Hitching.

Table 2. Scores for the Investigator's assessment of redness, swelling and hitching.

Score	**0**	**1**	**2**	**3**
Severity	None	Mild	Moderate	Severe

Frequency and means of scores will be presented separately by itching, redness, and swelling, by day and by treated thigh side.

9.3.3 *Physical examination*

Full physical examinations will be performed at the Screening (Day -15 to Day 0), Baseline (Day 0), Day 42 (EOS). Information about the physical examination will be recorded by the Investigator in the source documentation at the clinical Site. Any abnormalities will be recorded in the CRF. Significant findings/illnesses, reported after the start of the study and which meet the definition of an AE, will be recorded in the CRF.

Physical examination will be presented by time point through descriptive statistics. Frequency of abnormalities will be presented and compared by McNemar test, when applicable.

9.3.4 *Vital signs*

Subjects SBP/DBP (mmHg), HR (bpm), RF (bpm) and body temperature (°C) will be measured by the Investigator or his/her deputy after 5 min of rest (sitting position). The measurements will be performed at:

- Screening (Day -15 to Day 0);
- Baseline (Day 1: pre-dose, and 5 hours post-dose);

- Day 1;
- Day 14;
- Day 28 (EOT);
- Day 42 (EOS).

Descriptive statistics and change versus baseline by time point will be reported for each parameter. The values will be compared vs. pre-treatment values using ANOVA.

9.3.5 ECGs

A 12-leads ECG will be performed at Screening and Day 42 (EOS).

ECG assessment will be translate into: Normal, Abnormal NCR, and Abnormal CR.

ECGs will be summarized by presenting frequency tables of values falling outside normal ranges. Frequency of abnormalities will be compared by McNemar test, when applicable.

9.3.6 Clinical laboratory assays

Samples of blood (15 ml) and urine will be collected. The following laboratory analyses will be performed at Screening:

- **Hematology:** RBC, WBC and leukocyte differential count, platelet count, haemoglobin, MCV, MCH, MCHC, haematocrit;
- **Blood Chemistry:** total proteins, total bilirubin, alkaline phosphatase, AST, ALT, γ-GT, urea, creatinine, sodium, potassium, calcium, chloride, inorganic phosphorus, fasting glucose;
- **Urine drug screening**: presence of cannabinoids, opiates, cocaine, amphetamines, barbiturates, methadone and ecstasy;
- **Urinalysis:** Complete urinalysis and ioduria;
- **Virology:** HBs Ag, HCV Ab, HIV;
- **Thyroid**: TSH;
- **Pregnancy test.**

The following laboratory analyses will be performed at Baseline:

- **Thyroid**: T_4, T_3, rT_3 and TSH (T = 0);
- **Pregnancy test**.

The following laboratory analyses will be performed at Control 1, Control 2, Control 3, and EOT:

- **Thyroid**: T_4, T_3, rT_3 and TSH.

The following laboratory analyses will be performed at EOS:

- **Hematology:** RBC, WBC and leukocyte differential count, platelet count, haemoglobin, MCV, MCH, MCHC, haematocrit;
- **Blood Chemistry:** total proteins, total bilirubin, alkaline phosphatase, AST, ALT, γ-GT, urea, creatinine, sodium, potassium, calcium, chloride, inorganic phosphorus, fasting glucose;
- **Urinalysis:** complete urinalysis and ioduria;
- **Thyroid**: T_4, T_3, rT_3 and TSH.

All laboratory analyses will be encoded in: Normal, Abnormal NCR, Abnormal CR.

Laboratory data will be summarized by presenting frequency tables of values falling outside normal ranges. Frequency of abnormalities will be compared by McNemar test, when applicable. Moreover, for each parameter the descriptive statistics and change versus baseline by time point will be reported.

10 Summary of changes to the protocol

Analyses described in this statistical analysis plan are faithful to those specified in the protocol.

11 General Definitions

11.1 Computer systems and software to be used in the analysis

All statistical tests will be with a significance level of $\alpha = 0.05$, unless otherwise specified.

The results will be displayed and summarized in tables and figures.

Statistical analysis will be performed using SAS® version 9.4 for Windows® (SAS Institute Inc., Cary, North Carolina, United States).

11.1 Reporting conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001".

The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum

will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

11.2 Coding systems used

11.2.1 Clinical Terms

Clinical terms will be coded with MedDRA® (latest available version at the time of statistical analysis; version of coding dictionaries will be stated in the Study Report.

11.2.2 Drugs

Drugs will be coded using the Anatomical Therapeutic Chemical (ATC) Classification System.

11.3 Report type, language and format

The statistical output will be in Microsoft Word 2010 format and in English language.

12 Table and figures

12.1 Statistical analysis report

The set of tables, listings and figures (TLFs) produced in the statistical analysis and will follow sections 12.3, 12.4 and 12.5. These lists are intended to provide an overall idea of the general output, but they will not necessarily be reproduced.

12.2 Tables, headings and footnotes

All tables will be stratified by period, as appropriate. The tables repeated for analysis population will be produced only once if analysis populations are congruent.

Line 1: Study code:

Line 3: Table/Listing: Table name

Footnote: Date, draft/final version

12.3 List of Tables

1 Subject disposition
- 1.1 Overall subject disposition
- 1.2 Presence of subjects at study visits
- 1.3 Protocol violations

2 Demographics and baseline characteristics (by analysis population)
- 2.1 Demographics, pregnancy test, virology
- 2.2 Lifestyle characteristics: alcohol, smoke and urine drug at screening
- 2.3 Medical History and concomitant medications
- 2.4 Concomitant Medication

3 Primary endpoint
- 3.1 Free T4 by time point and change versus baseline

4 Secondary endpoints
- 4.1 rT3 by time point and change versus baseline
- 4.2 T3 by time point and change versus baseline
- 4.3 TSH by time point and change versus baseline

5 Safety analysis
- 5.1.1 Overview AE
- 5.1.2 Overview ADR
- 5.1.3 Overview SAE
- 5.2.1 Laboratory test: Hematology/ Chemistry by time point and change versus baseline
- 5.2.2 Laboratory test: Urinalysis by time point and change versus baseline
- 5.3.1 Vital Signs by time point and change versus baseline
- 5.4.1 ECG Overall investigator judgement by time point
- 5.5.1 Local Tolerability by PI: redness score frequency and statistics
- 5.5.2 Local Tolerability by PI: itching score frequency and statistics
- 5.5.3 Local Tolerability by PI: swelling score frequency and statistics
- 5.5.1 Local Tolerability by subject: redness score frequency and statistics
- 5.5.2 Local Tolerability by subject: itching score frequency and statistics
- 5.5.3 Local Tolerability by subject: swelling score frequency and statistics
- 5.6 Physical examination by study end versus baseline

12.4 Subject data listing

The following subject data listings will always contain the following key variables (KV): subject id, analysis population [safety, ITT, PP], visit, age at screening.

DISPOSITION OF SUBJECTS AND CORUSE OF STUDY

L1. Study visit

KV, date of informed consent, study dates by period

L2. Protocol violations

KV, protocol violations, reason, classification (minor, major)

BASELINE CHARACTERISTIC

L3. Demographic data

KV, height, weight, BMI, race

L4. Medical history

KV, system organ class, assessment, details, still present, comments

L5. Lifestyle characteristics: alcohol consumption

KV, alcohol test result, consume/day, beer, wine, spirit

L6. Lifestyle characteristics: nicotine consumption

KV, nicotine consumption, ex user/never, details

L7. Lifestyle characteristics: urine drug test

KV, test result, presence of

L8. Pregnancy test

KV, result, comment, contraception

L9. Virology: HBs Ag, HCV Ab, HIV

KV, test, value, unit, assessment

ELIGIBILITY

L10. Inclusion/Exclusion

KV, session, criteria number, text, result [yes/no]

L11. Concomitant medication

KV, drug, route, dose, unit, indication, start date, end/ongoing, related to.

L12. 3 months prior to the beginning of the study

KV, Blood donation, participation in the evaluation of any experimental drug

L13. Eligibility

KV, eligibility, date, investigator's name, investigator's signature

L14. Screening failure

KV, Screening failure, date, primary reason, comments

L15. Treatment administration

KV, Batch number, date, time

L16. Review of clinical symptoms and trial restriction

KV, new symptom, comments

L17. Trial restriction

KV, trial restriction, comments

ENDPOINTS

L18. Endocrinology: Free T4

KV, value, unit, assessment

L19. Endocrinology: rT3

KV, value, unit, assessment

L20. Endocrinology: T3

KV, value, unit, assessment

L21. Endocrinology: TSH

KV, value, unit, assessment

SAFETY

L22. Vital Signs

KV, date, parameters, result, unit.

L23. 12-lead ECG

KV, time, assessment, comments

L24. Physical examination

KV, system, assessment, comments

L25. Laboratory test: Haematology

KV, test, value, unit, assessment

L26. Laboratory test: Chemistry

KV, test, value, unit, assessment

L27. Laboratory test: Urinalysis

KV, date and time, assessment

L28. Laboratory test: loduria

KV, date and time, assessment

L29. Local Tolerability by investigator: redness

KV, zone, severity

L30. Local Tolerability by investigator: swelling

KV, zone, severity

L31. Local Tolerability by investigator: itching

KV, zone, severity

L32. Local Tolerability by subject: redness

KV, zone, treatment, NO specify, severity

L33. Local Tolerability by investigator: swelling

KV, zone, treatment, NO specify, severity

L34. Local Tolerability by investigator: itching

KV, zone, treatment, NO specify, severity

L35. Adverse events (if present)

KV, ID, description, onset date, end date, ongoing, serious, expected, correlated

L36. Serious Adverse events (if present)

KV, ID, description, details, onset date, end date, ongoing, severity, expectedness, seriousness, relationship, outcome, action taken, information drug, comments

END OF STUDY

L37. Subject's completion of study or premature discontinuation

KV, last day, completed, primary reason for withdrawal, discontinuation date, comments

L38. Diary verification

KV, date, name and signature of investigator's verification, health condition, concomitant medication

L39. Investigator's declaration

KV, date, name and signature of investigator's declaration

12.5 Figure

Figure 1 FT4 mean values and standard deviation

Figure 2 rT3 mean values and standard deviation

Figure 3 T3 mean values and standard deviation

Figure 4 TSH mean values and standard deviation

13 References

1 ICH Topic E3, Structure and Content of Clinical Study Reports, 30 November 1995.

2 ICH Topic E9, Statistical Principles for Clinical Trials, 5 February 1998.

16 APPENDICES

16.1 STUDY INFORMATION

16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used

DNV·GL

MANAGEMENT SYSTEM CERTIFICATE

Certificato No./Certificate No.:
CERT-04788-99-AQ-FLR-SINCERT

Data prima emissione/Initial date:
09 agosto 1999

Validità/Valid:
07 luglio 2017 - 07 luglio 2020

Si certifica che il sistema di gestione di/This is to certify that the management system of

Azienda Ospedaliera - Universitaria Pisana (AOUP)

U.O. Laboratorio Analisi Chimico-Cliniche:
Sede Principale: Via Paradisa, 2 - Edificio 2a/2b/31g - 56124 Pisa (PI) - Italy

È conforme ai requisiti della norma per il Sistema di Gestione Qualità/
has been found to conform to the Quality Management System standard:

UNI EN ISO 9001:2015 (ISO 9001:2015)

Valutato secondo le prescrizioni del Regolamento Tecnico RT-04/
Evaluated according to the requirements of Technical Regulations RT-04

Questa certificazione è valida
per il seguente campo applicativo:

Progettazione di nuovi servizi ed erogazione di servizi di analisi cliniche nei seguenti settori: biochimica clinica, ematologia, emocoagulazione e immunologia

(Settore EA: 38)

This certificate is valid
for the following scope:

Design of new services and provision of clinical services in the following fields: clinical biochemistry, hematology, hemocoagulation and immunology

(EA Sector: 38)

Luogo e Data/Place and date:
Vimercate, 13 luglio 2017

ACCREDIA
L'ENTE ITALIANO DI ACCREDITAMENTO

SQQ N° 003 A
SGA N° 003 D
SGE N° 007 H
SCR N° 004 F
EMAS N° 009 F
PRD N° 003 B
PRS N° 094 C
SSI N° 002 G

Membro di MLA EA per gli schemi di accreditamento SGQ, SGA, PRD, PRS, ISP, GHG, LAB e LAT, di MLA IAF per gli schemi di accreditamento SGQ, SGA, SSI, FSM e PRD e di MRA ILAC per gli schemi di accreditamento LAB, MED, LAT e ISP

Per l'Organismo di Certificazione/
For the Certification Body

Nicola Privato
Management Representative

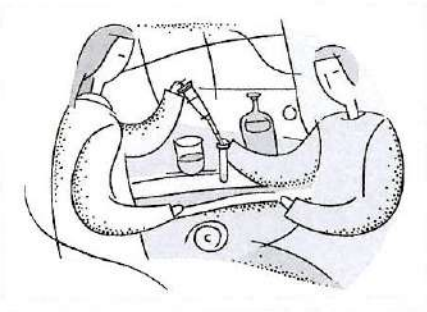
La validità del presente Certificato è subordinata al rispetto delle condizioni contenute nel Contratto di Certificazione/
Lack of fulfilment of conditions as set out in the Certification Agreement may render this Certificate invalid.
DNV GL Business Assurance Italia S.r.l. Via Energy Park, 14, 20871 Vimercate (MB), Italy. Tel: 039 68 99 905. www.dnvgl.it/assurance

Data della 1° APPLICAZIONE : 06.05.1999

REVISIONE N° 28	Firma	Revisione di esami e metodiche
del 15.01.2018	Casini Pellegrini	**Variazioni e integrazioni:** Inserimento esami S-Anticorpi anti Borrelia IgG, IgM (WB) ed eliminazione S-Anticorpi anti HSV IgM, S-Anticorpi anti HSV1 e 2 IgG, S-Anticorpi anti VZV IgM e IgG; cambiati gg lavorazione ACE; aggiunti TIBC e % saturazione; aggiunta nota ai vdr del d-dimero vidas; inserimento esami NSE, HE4, SCC, Ca72-4,Cy-fra 21-1, S100 e cambiamento gg di lavorazione e unità di misura; cambiati giorni di lavorazione Toxo e CMV; range del Fenobarbital .

Redazione			Verifica			Approvazione e diffusione		
Ruolo	Nome	DATA	Ruolo	Nome	DATA	Ruolo	Nome	DATA
Responsabili di Settore	Dott: Casini, Chiarugi, Leonildi, Malloggi, Moscato, Naldi, Ruocco,Salvadorini, Vacri, Vivaldi		Direttore Unità Operativa	Giovanni Pellegrini		Responsabile Assicurazione Qualità D.A.I. Medicina di Laboratorio	Paola Collecchi	

Copia controllata	X	Copia non controllata	



SOMMARIO DELLA SEZIONE B

ASSICURAZIONE DI QUALITA' 4

ELENCO DELLE ANALISI (*Valori di riferimento, Indagini microbiologiche*).....5

TABELLA DELLE METODICHE E DELLA PRECISIONE ANALITICA (CV%) 34

NOTE ESPLICATIVE PER LA RACCOLTA E L'INVIO DEI CAMPIONI.....46

Assicurazione di Qualità

La qualità dei risultati forniti dal Laboratorio di Cisanello è verificata mediante procedure quotidiane di Controllo e attestata dalla partecipazione a qualificati programmi di controllo esterno della qualità (VEQ), nazionali ed internazionali:

- Chimica Clinica (urgenze e routine): **Controllo Regione Toscana**
- **Chimica Clinica su urine: Controllo Biorad**
- **Proteine Specifiche: Controllo Regione Toscana**
- **Elettroforesi: Controllo Regione Toscana; EQAS elettroforesi (Instand e.V. Dusseldorf); EQAS-CNR Qualimedlab**
- **Esame urine: Controllo Nazionale Menarini**
- **HbA1C (Emoglobina glicata): Controllo Regione Toscana**
- **Marcatori Cardiaci: Controllo Regione Toscana**
- Ematologia: **Controllo Regione Toscana; TQ, Dics**
- Coagulazione: **Controllo Nazionale IL, Controllo Regione Toscana; VEQ F.C.S.A.; UK NEQAS**
- Sierologia: **Controllo Regione Toscana**

ELENCO DELLE ANALISI

Per una consultazione più semplice l'elenco delle analisi è stato suddiviso in colonne

La prima colonna a sinistra (esame) riporta in ordine alfabetico il nome dell'analisi o del test così come compare sul referto.

La seconda colonna (valore di riferimento) riporta gli intervalli di riferimento dell'analisi; per i farmaci vengono riportati gli intervalli terapeutici;

La terza colonna (unità di misura) riporta l'unità di misura utilizzata per l'analisi o per il test.

La quarta colonna (tempi di risposta) riporta i tempi di risposta in giorni, per ciascuna analisi.
Le caselle corrispondenti alle analisi per le quali è prevista la consegna in giornata sono state lasciate vuote, per una più rapida consultazione. Il tempo di risposta relativo agli esami urgenti è immediato (tempo tecnico di esecuzione del test).

La quinta colonna (colore dei tappi) riporta il colore del tappo della provetta, per un corretto prelievo.
I colori si riferiscono agli esami in programmazione ordinaria, mentre gli esami urgenti devono essere inviati nelle provette con tappo verde chiaro – litio eparina, ad eccezione dell'Emocromo (tappo viola); PT, PTT, Fibrinogeno, Dimero D (tappo celeste); Ammonio e BNP (tappo verde scuro)

La sesta colonna (sinonimi) riporta eventuali sinonimi o il nome di alcuni esami comunemente indicati con sigle. Sono inoltre indicati quegli esami assimilabili per significato diagnostico.

La settima e ultima colonna (note) è riservata ad eventuali note aggiuntive per una corretta interpretazione dei risultati analitici . Le note relative a particolari modalità di prelievo sono indicate con un numero, mentre ulteriori informazioni sono indicate con lettere dell'alfabeto. Tutte le note sono descritte in dettaglio a partire da pag. 44.

VALORI DI RIFERIMENTO DEGLI ESAMI DI LABORATORIO

Laboratorio di Analisi Chimico-cliniche e Microbiologiche -Cisanello

LEGENDA: S=siero, P=plasma,	U=urine, F=feci	SI=sangue intero	
CHIMICA – VERDE	CHIMICA: ELETTROFORESI, PROTEINE SPECIFICHE E AUTOIMMUNITA' - BIANCO	SIEROLOGIA - GIALLO	EMATOLOGIA LILLA COAGULAZIONE - CELESTE

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-ACE	65.8 – 114.4	U/L	**10**	verde		
S-Acidl biliari	≤ 10	µmol/L	**3**	marrone	Sali biliari	
P-Acido urico	maschio 3,5 - 7,0 femmina 2,5 - 6,0	mg/dL		verde	Uricemia	
U-Acido urico	37 – 92 (urine prima mattina) 200-1000	mg/dL mg/24 h		Urine tappo giallo	Uricuria	6
S-Agglutinine a freddo	Assenti	Titolo	**2**	giallo		
P-Aggregazione piastrinica **ADP 2 µM** **ADP 10 µM** **Collageno 5 µM** **Acido arachidonico** **Ristocetina** **Cofattore ristocetinico**	 20 - 70 60 – 100 60 – 100 65 – 95 65 – 95 ➢ 69	%	**3**	blu (3 provette)	AGG	5 24

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Albumina	3,5 - 5,0	g/dL		verde		
P-Albumina urgente	3,5 - 5,0	g/dL		verde		
P-Aldolasi	< 7,6	U/L	**2**	verde		
S- α 1 antitripsina	90 - 200	mg/dL	**5**	bianco grande	AAT	
P- α 1 glicoproteina acida	50 - 120	g/L		verde	Mucoproteine, Siero mucoidi	
S- AFP	Adulti: < 7,0 Sett. gestaz. mediana 14 25,3 15 29,0 16 33,3 17 38,3 18 44,0 19 54,8	µg/L	**2**	Rosso 9 mL	Alfafetoproteina	
P-Amilasi	28 - 100	U/L		verde		
P-Amilasi urgente	28 - 100	U/L		verde		
P-Amilasi pancreatica	15 - 53	U/L		verde		
U-Amilasi	< 460	U/L		Urine tappo giallo		6
P-Ammonio	maschio fino a 102 femmina fino a 87	µgl/dL		Verde scuro		5,8,19, 19

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
S-Anti Beta 2 glicoproteina (IgG, IgM)	IgM < 15 IgG < 15	U/mL	**15**	Bianco piccolo	AB2GPI	
P-Antiplasmina	70 - 130	%	**5**	blu	AP	2, 5
S-Anti Protrombina (IgG, IgM)	IgM < 15 IgG < 15	U/mL	**15**	Bianco piccolo		
S-Antistreptolisina O	< 250	UI/mL	**5**	bianco grande		
P-Antitrombina	83 - 128	%		celeste	AT	2
P-Apixaban dosaggio antiXa	Non specificabile	ng/mL	2	blu (3 provette)	Eliquis	2,5, 27
S-Apolipoproteina A1	95 - 230	mg/dL	**5**	bianco grande	Apo A1	
S-Apolipoproteina B	55 - 165	mg/dL	**5**	bianco grande	Apo B	
S-Aptoglobina	30 - 200	mg/dL	**5**	bianco grande		
S-β2 microglobulina	200 - 2000	mg/dL	**5**	bianco grande		

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
S-β HCG (per espianto)	Adulti:< 2; pre-men. < 1.0; post-men. <7.0 Gestazione Range valori 3 - 6 settimane 5.8 - 31795 7 – 10 settimane 3697 - 186977 12 - 13 settimane 27832 - 210612 14 - 15 settimane 12039 – 70971 16 – 18 settimane 9040 - 58176	mUI/mL		giallo	Gonadotropina corionica	
S-IgG anti Bartonella henselae e quintana	Negativo	DO	**30**	giallo		
S-IgM anti Bartonella henselae e quintana	Negativo	DO	**30**	giallo		
P-Bicarbonati (urgente)	22 - 30	mmol/L		verde	CO_2	
P-Bicarbonati	22 - 30	mmol/L		verde	CO_2	
P-Bilirubina diretta	Fino a 0,3	mg/dL		verde		
P-Bilirubina totale	Fino a 1,2	mg/dL		verde		
P-Bilirubina diretta (urgente)	Fino a 0,3	mg/dL		verde		
P-Bilirubina totale (urgente)	Fino a 1,2	mg/dL		verde		
BNP (urgente)	< 100	Pg/mL		Verde scuro		23
S-Anticorpi anti Bordetella pertussis IgG, IgM	Negativo	DO	**15**	giallo		
S-Anticorpi anti Borrelia IgG, IgM	Negativo	DO	**12**	giallo		
S-Anticorpi anti Borrelia IgG, IgM (WB)	<=5 Negativo 6 Dubbio >=7 Positivo	R. INT.	**30**	giallo		
P-ProBNP	< 125 CUT-OFF pazienti ambulat. < 300 CUT-OFF pronto soccorso	ng/L	**5**	verde		
S-CA 19.9	< 39	KU/L	**2**	Rosso 9 mL		
S-CA 125	< 35	KU/L	**2**	Rosso 9 mL		
S-CA 15.3	< 25	KU/L	**2**	Rosso 9 mL		
S-CA 72.4	< 6,9	KU/L	**7**	Rosso 9 mL		

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Calcio	maschio femmina 0 – 1 a 8,4 – 10,8 8,4 – 10,8 2 – 4 a 8,4 – 10,4 8,4 – 10,4 5 – 15 a 9,2 – 11,0 9,2 – 11,0 > 15 a 8,6 – 10,2 8,6 – 10,2	mg/dL		verde		
P-Calcio (urgente)	maschio femmina 0 – 1 a 8,4 – 10,8 8,4 – 10,8 2 – 4 a 8,4 – 10,4 8,4 – 10,4 5 – 15 a 9,2 – 11,0 9,2 – 11,0 > 15 a 8,6 – 10,2 8,6 – 10,2	mg/dL		verde		
U-Calcio	5,2 – 35,7 (urine prima mattina) 100 - 321	mg/dL mg/24h	Urine tappo giallo			6
S-Catene leggere κ	170 – 370	mg/dL	**5**	bianco grande		
S-Catene leggere λ	90 - 210	mg/dL	**5**	bianco grande		
U-Catene leggere κ	fino a 1	mg/dL	**5**			
U-Catene leggere λ	fino a 0,5	mg/dL	**5**			
S-CEA	< 5,2	µg/L	**2**	Rosso 9 mL	Ag carcinoembrionale	
S-Ceruloplasmina	20 - 60	mg/dL	**5**	bianco grande		
S-Cystatina C	0,6 – 1,45	mg/L	**5**	bianco grande		

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
S-Anticorpi anti-Citomeg. IgM	< 0,85 : Negativo > 1,00: Positivo 0,85 – 1,00: non conclusivo	Indice	**3**	giallo	CMV IgM	
S-Anticorpi anti-Citomeg. IgG	< 6,0: Negativo >15,0 : Positivo 6 – 15,0: non conclusivo	UA/mL	**3**	giallo	CMV IgG	
P-CK	maschio 10 - 190 femmina 10 - 170	U/L		verde	Creatin-fosfochinasi	
P-CK (urgente)	maschio 10 - 190 femmina 10 - 170	U/L		verde	Creatin-fosfochinasi	
P-CK-MB in massa (urgente)	maschio fino a 4,94 femmina fino a 2,88	µg/L		verde		
P-CK-MB in massa	maschio fino a 4,94 femmina fino a 2,88	µg/L		verde		
S-Anticorpi anti Chlamydia pneumoniae – trachomatis IgG, IgM	Negativo	DO	**12**	giallo		
Clearance creatinina	maschio 71 - 151 femmina 71 - 151	mL/min				6.7 d
Clearance urea	41 - 65	mL/min				6,7, e
P-Cloro	95 - 110	mEq/L		verde	Cl, Cloruri	
P-Cloro (urgente)	95 - 110	mEq/L		verde	Cl, Cloruri	
U-Cloro	46 – 168 (urine prima mattina) 110 - 250	mEq/L mEq/24h		Urine tappo giallo	Cl	6

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Colesterolo	< 200	mg/dL		verde		
P-Colesterolo HDL	U.> 40 D.> 45	mg/dL		verde	HDL	
P-Colesterolo LDL	valore raccomandato < 130 moderatamente elevato 130 - 160 elevato > 160	mg/dL		verde	LDL	
P-Colinesterasi **P-Colinesterasi (urgente)** **P-Colinesterasi inibita** **Numero di dibucaina**	5300 - 12900 500 - 3000 > 72	U/L % 		verde verde verde 	CHE CHE-I Dibucaina	
S-Complemento C3c	90 - 180	mg/dL	**5**	bianco grande	C3	
S-Complemento C4	10 - 40	mg/dL	**5**	bianco grande	C4	
P-Complessi trombina-antitrombina TAT	1 - 4,0	µg/L	**15**	blu	TAT	2,5
S-Anticorpi anti Coxiella b. IgG, IgM	Negativo	DO	**15**	giallo		

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Creatinina	maschio femmina < 3 a 0.24 – 0.41 0.24 – 0.41 3 - 5 a 0.31 – 0.47 0.31 – 0.47 6 - 7 a 0.32 – 0.59 0.32 – 0.59 8 - 9 a 0.40 – 0.60 0.40 – 0.60 10 - 11 a 0.40 – 0.73 0.40 – 0.73 12-13 a 0.53 – 0.79 0.53 – 0.79 14-15 a 0.57 – 0.87 0.57 – 0.87 > 15 a. 0,7 – 1,20 0,5 – 0,90	mg/dL		verde		
e-GFR	144* (Crea $^{-0.329}$)*(0.993 ^{età})/0.7 calcolo eGFR per Crea <=0.7 e sesso F e 18<età<75 144* (Crea $^{-1.209}$)*(0.993 ^{età}) /0.7 calcolo eGFR per Crea >0.7 e sesso F e 18<età<75 141* (Crea $^{-0.411}$)*(0.993 ^{età}) /0.9 calcolo eGFR per Crea <=0.9 e sesso M e 18<età<75 141* (Crea $^{-1.209}$)*(0.993 ^{età}) /0.9 calcolo eGFR per Crea >0.9 e sesso M e 18<età<75 3736* (Crea $^{-0.87}$)*(0.95 ^{età}) calcolo eGFR per età>75aa e sesso M 3736* (Crea $^{-0.87}$)*(0.95 ^{età})*0.82 calcolo eGFR per età>75aa e sesso	mg/dL		verde		
U-Creatinina	(urine prima mattina) 35 - 259 (uomini) 28 - 217 (donne) 1040 - 2350 (uomini) 740 - 1570 (donne)	mg/dL mg/24h mg/24h		Ue tappo giallo		6

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
S-Crioglobuline	Negativo		**6**	giallo		
S-Curva glicemica: basale a 120'	74 - 109 < 140	mg/dL		grigio	Curva da carico	4, 9, 10
S-Curva glicemica in gravidanza: **basale** **a 60'** **a 120'**	< 92 < 180 < 153	mg/dL		grigio		
S-Cy-fra 21.1	< 3,3	µg/L	**7**	Rosso 9 mL		
P-Dabigatran dosaggio ECA	Non specificabile	ng/mL	**2**	blu (3 provette)	pradaxa	2,5, 27
P-Dabigatran dosaggio dTT	Non specificabile	ng/mL	**2**	blu (3 provette)	pradaxa	2,5, 27

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Dimero D in urgenza	< 0,3 (limite di negatività) Per esclusione della trombosi venosa profonda. Valori superiori sono osservabili in soggetti sani (Contraccezione, gravidanza, attività fisica, stress, anziani...)	mg/L		celeste	D-D	2 a,f
P-Dimero (ELFA) in routine	Per esclusione della trombosi venosa profonda: - soggetto di età= < 50 anni: cut-off = 0.5mg/L - Soggetto di età > 50 anni: cut-off = età x 0.1mg/ (esempio: a 65 anni il cut-off da utilizzare sarà = 0.65mg/L) Valori superiori sono osservabili in soggetti sani (Contraccezione, gravidanza, attività fisica, stress, anziani...)	mg/L	**1**	blu	D-D	2 a,f
S-Anticorpi anti EBV VCA IgG, IgM	Negativo	KUA/L	**5**	giallo		
S-Anticorpi anti EBV EBNA IgG	Negativo	KUA/L	**5**	giallo		
S-Anticorpi anti EBV EA IgG	Negativo	KUA/L	**5**	giallo		
S-Elettroforesi proteica				bianco piccolo	Proteine frazionate Protidogramma	
Albumina %	55,8 – 66,1	%				
α 1 globuline %	2,9 – 4,9	%				
α 2 globuline %	7,1 –11,8	%				
β1 globuline %	4,7 – 7,2	%				
β2 globuline %	3,2 – 6,5	%				
γ globuline %	11,1 – 18,8	%				

esame	valore di riferimento				unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
Esame emocromocitometrico	F ≤ 14	F > 14	M ≤ 14	M > 14			lilla piccolo		1, 22
Leucociti	4,0 – 11	4,0 – 11	4,0 – 11	4,0 – 11	x10^3/µL			WBC	
Eritrociti	4,2 - 5,4	4,2 - 5,4	4,5 – 6,0	4,5 – 6,0	x10^6/µL			RBC	
Emoglobina	11,5 - 16,0	11,5 - 16,0	13,0 - 18,0	13,0 - 18,0	g/dL			Hb	
Ematocrito	37 - 47	37 - 47	41 - 50	41 - 50	%			Hct, Ht, PCV	
Vol. Corpuscolare Medio	80 – 100	80 – 100	80 – 100	80 – 100	fL			MCV	
Cont. Emogl. Corp. Medio	26 - 33	26 - 33	26 - 33	26 - 33	pg			MCH	
Conc. Emogl. Corp. Media	31 - 36	31 - 36	31 - 36	31 - 36	g/dL			MCHC	
Anisocitosi Eritrocitaria	11.5 – 15.0	11.5 – 15.0	11.5 – 15.0	11.5 – 15.0	%			RDW	
Piastrine	140 - 450	140 - 450	140 - 450	140 - 450	x10^3/µL			PLT	
Vol. Piastrinico Medio	8,0-11,9	8,0-11,9	8,0-11,9	8,0-11,9	fL			MPV	
G.neutrofili %	30-55	40-75	30-55	40-75	%				
Linfociti %	30-50	20-50	30-50	20-50	%				
Monociti %	2-13	2-13	2-13	2-13	%				
G.eosinofili %	< 5	< 7	< 5	< 7	%				
G.basofili %	< 0,5	< 1	< 0,5	< 1	%				
G.neutrofili	1,5-8	1,8-7,5	1,5-8	1,8-7,5	x10^3/µL				
Linfociti	1,5-7,3	0,9-5	1,5-7,3	0,9-5	x10^3/µL				
Monociti	< 0,9	0,1-1	< 0,9	0,1-1	x10^3/µL				
G.eosinofili	< 0,7	< 0,7	< 0,7	< 0,7	x10^3/µL				
G.basofili	< 0,1	< 0,1	< 0,1	< 0,1	x10^3/µL				

esame	valore di riferimento				unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
Esame emocromocitometrico (segue da pagina precedente)	F ≤ 14	F > 14	M ≤ 14	M > 14			lilla piccolo		1, 22
Granulociti immaturi	0	0	0	0	%				
Eritroblasti	0	0	0	0	x10^3/µL				
Schistociti	< 0,25	< 0,25	< 0,17	< 0,17	%				
Piastrine reticolate	0,85-5,39	0,85-5,39	0,85-5,39	0,85-5,39	%				

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
SI-Emoglobina glicata	20 - 38	mmol/mol		Verde scuro	Hb A1C	
S-Anticorpi anti Entamoeba IgG	Negativo	DO	**15**	giallo		
P-Anticorpi anti eparina / PF4 - HIT	≤ 1,0	U/mL	**2**	blu	Anti PF4 / HIT	5 27
P-Eparina dosaggio/attività anti Xa	0,5 – 1,0 (profilassi e terapia Dalteparina) 0,2 – 1,0 (profilassi Fondaparinux) 1,0 – 2,0 (terapia Fondaparinux)	UI/mL Mg/L	**2**	blu	attività anti Xa	g 27
Esame standard delle Urine				Urine tappo rosso		
Colore	paglierino					
Aspetto	limpido					
Peso specifico	1,015 - 1,025					
pH	5,5 – 7,0					
Glucosio	assente	mg/dL				
Albumina	< 15	mg/dL				
Chetoni	assente					
Urobilinogeno	≤ 0.2	EU/dL				
Bilirubina	assente	mg/dL				
Emoglobina	assente					
Nitriti	assente					
Esame del Sedimento:						
Emazie	0 – 16	µL				
Leucociti	0 – 20	µL				
Cellule epiteliali	0 – 40	µL				
Cilindri	0 – 3	µL				
Cristalli	0 – 20	µL				

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Fattore coagulativo Vc (per trapianti)	69 - 139	%	**7**	blu	FVc	2, 5
P-Fattore di crescita placentare Solubile fms-simil tirosina-kinasi (sFlt-1) sFlt/PIGF ratio	PRECLAMPSIA A ESORDIO PRECOCE: **≥ 85** diagnosi **38-85** predizione di comparsa entro le 4 sett. succ. **< 38** predizione di esclusione per la1° sett. succ. PRECLAMPSIA TARDIVA: **≥ 110** diagnosi **38-110** predizione di comparsa entro le 4 sett. succ. **< 38** predizione di esclusione per la1° sett. succ.		**3**	bianco	PIGF	
S-Fattore reumatoide	< 15	UI/mL	**5**	bianco grande	FR, Reuma-test	
S-Ferritina	maschio 30 - 400 femmina 13 – 150	µg/L	**2**	Rosso 9 mL		
P-Ferro	33 - 193	µg/dL		verde	Sideremia	
P-Fibrinogeno Clauss	200 - 400	mg/dL		celeste	FIB	2

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
S-Folato	3.89 - 26.8	µg/L	2	Rosso 9 mL		
P-Fosfatasi alcalina P-Fosfatasi alcalina (urgente)	30 - 130	U/L		verde verde	ALP, PAL	
U-Fosfatasi alcalina	< 20	U/L				
P-Fosforo	2.5 – 4.5	mg/dL		verde	P	
P-Fosforo (urgente)	2.5 – 4.5	mg/dL		verde	P	
U-Fosforo	40 - 140 (urine prima mattina) 400 - 1300	mg/dL mg/24h		Urine tappo giallo		6
P-Frammento protrombinico 1 + 2	69 - 229	Picomoli / L	5	blu	F1 + 2	2, 5
P-Fruttosamina	205 - 285	µmol/L		verde		
S-FTA-ABS (IFA)	NEGATIVO	titolo	15	giallo		
-γGT	maschio < 60 femmina < 40	U/L		verde	Gammaglutamiltransferasi	
P-γGT (urgente)	maschio < 60 femmina < 40	U/L		verde	Gammaglutamiltransferasi	

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
Glicosuria frazionata (ore: 08 - 13 / 13 - 20 / 20 - 08)	0 - 20	mg/dL				9, 10
P-Glucosio	74 - 109	mg/dL		verde	Glicemia	11
P-Glucosio (urgente)	74 - 109	mg/dL		verde	Glicemia	11
U-Glucosio	0 - 20	mg/dL			Glicosuria	6
S-He4	Pre-menopausa <70 Post-menopausa <140	pmol/L	**3**	Rosso 9 mL		
F-Helicobacter pylori (ricerca antigene)	negativo	DO	**4**		HPSA	
S- HIV 1-2 Ab e Ag	negativo	S/CO	**2**	giallo		
S-HTLV I-II	negativo	S/CO	**2**	giallo		
S-IgG	700 – 1600	mg/dL	**5**	bianco grande		
S-IgA	70 – 400	mg/dL	**5**	bianco grande		
S-IgM	40 - 230	mg/dL	**5**	bianco grande		
S-IgE totali	50 - 120	UI/mL	**5**	bianco grande		
Immunofissazione sierica e urinaria	valutazione qualitativa del tracciato (assenza di comp. monoclinali)		**12**	bianco piccolo	IFE	

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Lattato	4,5 – 19,8	mg/dL		grigio	Acido lattico	4
S-Anticorpi anti Leishmania Ig totali	Negativo	DO	**15**	giallo		
P-LDH P-LDH (urgente)	Bambini (< 15 a.) 120 – 300 Adulto (≥ 15 a.) maschio 135 - 225 femmina 135 - 214	U/L		verde verde	Latticodeidrogenasi	
P-Lipasi	Fino a 60	U/L		verde		
P-Lipasi (urgente)	Fino a 60	U/L		verde		
S-Lipoproteina a	30	mg/dL	**5**	bianco grande	Lp(a)	
S-Anticorpi anti Legionella pn. Ig totali	Negativo	DO	**15**	giallo		
S-LAC Screening fosfolipidi (ELISA IgG)	negativo		**10**	Bianco piccolo	LAC-aPL, LAC ELISA screening. fosfolipidi	
P-Lupus anticoagulant (Screening) **Se positivo lo Screening si procede con:** **P-Lupus anticoagulant veleno di vipera Russel** **P-Lupus anticoagulant dRVVT + fosfolipidi** **P-Lupus anticoagulant silica clotting time**	negativo		**5**	blu	LAC-dRVVT, LAC-SCT	2

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
S- Ab Anti Leptospira IgG	Negativo	titolo	30	giallo		
S- Ab Anti Leptospira IgM	Negativo	titolo	30	giallo		
S- Ab totali Anti Listeria monocytogenes	Negativo	DO	30	giallo		
P-Magnesio (routine e urgenza)	1.7 – 2.5	mg/dL		verde	Mg	
U-Magnesio	4,1 – 13,8 (urine prima mattina) 60 - 210	mg/dL mg/24h		Urine tappo giallo		6
SI-Malaria (test rapido)	negativo			viola		
Markers Epatite A **S-HAV IgM, Ig totali**	negativo	S/CO	**2**	giallo	HAV	
Markers Epatite B				giallo	HBV	
S-HBsAg quantitativo	< 0,05	KUI/L	**2**			
S-HBsAg	< 1,0 negativo.; ≥1,0 positivo	S/CO	**2**			
S-AntiHBs	< 10 ass. risp. antic.; ≥10 ind. risp. antic.	UI/L				
S-HBeAg	< 1,0 negativo.; ≥1,0 positivo	S/CO				
S-Anti Hbe	< 1,0 positivo.; ≥1,0 negativo	S/CO				
S-Anti Core Ig totali	< 1,0 negativo.; ≥1,0 positivo	S/CO				
S-Anti Core IgM	< 1,0 negativo.; ≥1,0 positivo					

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
Markers Epatite C **S-Anti HCV Ig totali**	negativo	S/CO	**2**	giallo	HCV	c
S- HCV Core Ag	< 0,06 negativo ≥ 0,06 positivo	ng/L	**2**	giallo	Antigene HCV	
S-Anti HCV IgM	negativo	DO	**10**	giallo		
S- Anti HCV di conferma	negativo	R. INT.	**30**	giallo		
Markers Epatite D (S-Anti Delta Ig totali) **Markers Epatite D (S-Anti Delta IgMi)**	Negativo negativo	DO DO	**15** **15**	giallo	HDV HDV-M	
S-Ac anti Mycoplasma pn. IgG, IgM	negativo	DO	**12**	giallo		
U-Microalbumina	< 30	mg/L		Urine tappo giallo	Microalbuminuria	6
U-Microalbumina / Creatinuria	< 30 normoalbuminuria 30 – 299 microalbuminuria >= 300 macroalbuminuria	mg/g				6
P-Mioglobina	maschio 28 - 72 femmina 25 - 58	µg/L		verde		
S-Monotest	negativo		**2**	giallo	Mononucleosi	
S-NSE	< 16,3	µg/L	**3**	Rosso 9 mL		
P-Omocisteina (basale) **Curva da carico con metionina:** **P-Omocisteina dopo 240'** **P-Omocisteina incremento a 4 ore** **P-Omocisteina, incremento a 6 ore**	maschio 4,3 – 11,1 femmina 4,3 – 11,1 < 38 < 35 < 28 < 24 < 27 < 27	µmol/L µmol/L µmol/L µmol/L	**1** **2** **2** **2**	blu	OMO	5, 19, 24
S-Osmolalità	280 - 295	mOsm/kg H2O		verde		3
U-Osmolalità	300 - 800	mOsm/kg H2O				

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Plasminogeno	75 - 150	mg/dL	**5**	blu	Pl	2, 5
P-Plasminogeno, attivat. tissutale / dosaggio antigenico	< 10	ng/mL	**5**	blu	tPA Ag	5
P-Plasminogeno, inibitore dell'attivatore tissutale / dosaggio antigenico	1 - 25	ng/mL	**5**	blu	PAI1 Ag	5
P-Plasminogeno, inibitore dell'attivatore tissutale / dosaggio attività	< 5	ng/mL	**5**	blu	PAI1 Att.	5
P-Potassio	3.5 – 5.1	mEq/L		verde	K, caliemia	
P-Potassio (urgente)	3.5 – 5.1	mEq/L		verde	K, caliemia	
U-Potassio	20 – 80 (urine prima mattina) 25 - 125	mEq/L mEq/24h				6
S- Procalcitonina	< 0,5	ng/mL		verde		
P-Proteina C (resistenza alla)	2,61-3,32	sec	**7**	blu	APCR, Resistenza PC attivata, FV° Leiden.	2,5
P-Proteina C	70 - 140	%	**7**	blu	PC	2,5
P-Proteina S (libera – quantitativa)	74,1 - 146,1 (uomo) 54,7- 123,7 (donna)	%	**7**	blu	PS	2, 5
P-Proteina C reattiva	< 0,5	mg/dL		verde	PCR	
P-Proteina C reattiva (urgente)	< 0,5	mg/dL		verde	PCR	
S-Proteina C reattiva ultrasensibile	Fino a 5	mg/L	**5**	bianco grande	PCR ultrasensibile	

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Proteine totali	6.0 – 8.2	g/dL		verde		
P-Proteine totali (urgente)	6.0 – 8.2	g/dL		verde		
U-Proteine totali	< 15 (urine prima mattina) < 150	mg/dL mg/24h		Urine tappo giallo		6
S-PSA	< 4	µg/L	2	Rosso 9 mL	Ag prost. specifico	
S-PSA libero		µg/L	2	Rosso 9 mL		
S-PSA libero/PSA totale	0,18 – 1,0		2	Rosso 9 mL		
S-Recettore solubile della transferrina	800 - 1800	µg/L	5	bianco grande		

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
SI-Reticolociti	0,5 – 2,5	%		lilla piccolo		1
SI Reticolociti sottopopolazioni:						
SI Reticolociti totali	22 – 139	x 10^9/L				
SI- Immaturi		%				
SI-Reticolociti (concentrazione Hb)	28,2 – 35,7	pg				
S-Anticorpi anti Rickettsia IgG, IgM	Negativo	DO	**15**	giallo		
S- Ab Anti Rickettsia tiphy IgG, IgM	Negativo	titolo	**30**	giallo		
P-Rivaroxaban dosaggio antiXa	Non specificabile	ng/mL	**2**	blu (3 provette)	Xarelto	2,5, 27
S-Anticorpi anti-Rosolia IgM	< 0,800 : Negativo > 1,000 : Positivo 0,800 – 0,999 : non conclusivo	Indice	**3**	Rosso 9 mL	Rubeo-test	
S-Anticorpi anti-Rosolia IgG	< 10,0 : Negativo > 10.0: Positivo	KUI/L	**3**	Rosso 9 mL	Rubeo test	
S-RPR	Negativo	titolo	**6**	giallo	VDRL	
S-pS100	< 0,105	µg/L	**7**	Rosso 9 mL		
S-SCC	< 1,5	µg/L	**3**	Rosso 9 mL		
S-Sieroamiloide A	Fino a 6,4	µg/mL	**5**	bianco grande	SAA	

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
Sierodiagnosi Weil-Felix	negativo	Titolo	**2**	giallo	Sierol. per Rickettsiosi	
Sierodiagnosi Widal-Wright	negativo	Titolo	**2**	giallo	Sierologia per Tifo, Paratifo, Brucella	
S-Sifilide (Screening) **S-Sifilide (Test di conferma) IgG** **S-Sifilide (Test di conferma) IgM**	< 1: negativo ≥ 1: positivo negativo negativo	S/CO DO DO	**2** **7** **7**	giallo giallo giallo	Sierologia per lue	
P-Sodio	135 - 145	mEq/L		verde	Na	
P-Sodio (urgente)	135 - 145	mEq/L		verde	Na	
U-Sodio	54 – 190 (urine prima mattina) 40 - 220	mEq/L mEq/24h		Urine tappo giallo		6
P-Tempo di protrombina **P-Tempo di protrombina (Pazienti in TAO)**	80 – 130 0,81 – 1,2 2 – 3	% PT ratio INR		Celeste Blu	PT, Attività protrombinica	2
P-aPTT **P-aPTT ratio**	25,1 – 36,5 0,84 – 1,22	sec. ratio		celeste	Tempo di tromboplastina parziale attivato	2
P-Tempo di Trombina	10,03 – 16,6 0,76 – 1,2	Sec. ratio		celeste	TT	2
P-Aptt fase di contatto (10min)	25,1 – 36,5 0,84 – 1,22	Sec. ratio		blu	aPTT per precallicreina/kininogeno	2

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
Test di gravidanza (urine)				giallo		
S-Ac anti Tossina tetanica	< 0.1: nessuna protezione 0.11 – 1.0 protezione sufficiente 1.1 – 5.0 protezione a lungo term.	KUI/L	**14**	giallo		
S-Anticorpi anti-Toxoplasma IgM	< 0,800 : Negativo > 1,000 : Positivo 0,800 – 0,999 : non conclusivo	Indice	**3**	Rosso 9 mL	Toxo-test	
S-Anticorpi anti-Toxoplasma IgG	< 1,0 : Negativo > 3,0 : Positivo > 1,0 - <3,0 : non conclusivo	KUI/L	**3**	Rosso 9 mL	Toxo-test	
S- TPHA	negativo	titolo	**6**	giallo		
P-Troponina T HS (ultrasensibile)	< 14	ng/L		verde	cTnT	
P-Transaminasi GO	maschio < 45 femmina < 40	U/L		verde	AST, Aspartato-aminotransferasi	
P-Transaminasi GO (urgente)	maschio < 45 femmina < 40	U/L		verde		
P-Transaminasi GP	maschio < 40 femmina < 40	U/L		verde	ALT,Alanino-amino-transferasi	
P-Transaminasi GP (urgente)	maschio < 40 femmina < 40	U/L		verde		

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Transferrina	2,0 - 3,6	g/L		verde		
P-TIBC (Transferrinax1,25)	2,86-5,15			verde		
% saturazione Sideremia/(Transferrinax1,42)x100	15-45			verde		
S-Transferrina desialata	0 – 1,5	%	**5**	Bianco grande	CDTest	
P-Trigliceridi	< 150	mg/dL		verde		
S - Anticorpi anti tripanosoma cruzii	< 0,800 : Negativo > 1,000 : Positivo 0,800 – 0,999 : non conclusivo	S/CO	**5**	giallo	Malattia di Chagas	
P-Urea **BUN**	10 – 50 < 23	mg/dL		verde	(Azotemia)	
P-Urea (urgente) **BUN**	10 – 50 < 23	mg/dL		verde	(Azotemia)	
U-Urea	900 – 3000 (urine prima mattina) < 35	mg/dL g/24h		Urine tappo giallo	Azoturia	6
VES	maschio < 25 femmina < 30	mm / h		lilla	Velocità di eritrosedimentazione	1
S-Vitamina B12	191 - 663	ng/L	**2**	Rosso 9 mL	Cobalamina	
S-B 12 Attiva (Holo-TC)	20,6-196,7	pmol/L	**2**	Giallo	Holotranscobalamina	

VALORI DI RIFERIMENTO DEGLI ESAMI DI LABORATORIO
Laboratorio di Analisi Chimico-cliniche - Cisanello

LEGENDA: S=siero, P=plasma, | U=urine, F=feci | Sl=sangue intero

FARMACI

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
P-Acido valproico	50 - 100	µg/mL		marrone	valproato	
U- Barbiturici	< 200 (negativo)	ng/mL	3			
S- Barbiturici		ng/mL		marrone		
U- Benzodiazepine	< 200 (negativo)	ng/mL	3			
S- Benzodiazepine		ng/mL		marrone		
P-Carbamazepina	4 - 12	µg/mL		marrone		
P-Digossina	0.80 - 2.00	µg/L		marrone		
P-Digossina urgente	0.80 – 2.00	µg/L		marrone		
P-Etanolo	0 – 0.5	g/L		Verde scuro	Alcoolemia	8, 5, 25
S-Litio	< 1.2	mEql/L		Marrone grande		
P-Fenitoina	10 - 20	µg/mL		marrone		
P-Fenobarbital	10 - 40	µg/mL		marrone		
P-Paracetamolo	10 - 30	µg/mL		marrone	Acetominofene	
P-Salicilati	Fino a 30	mg/dL		marrone		
P-Teofillina	10 – 20	mg/L		marrone		
P-Teofillina urgente	10 – 20	µg/mL		marrone		
P- Triciclici (antidepressivi)		ng/mL		marrone		b
S-Vancomicina	5 - 40	µg/mL		marrone		

DROGHE

esame	valore di riferimento	unità di misura	tempi di risposta	colore dei tappi	sinonimi e acronimi	note
U-Amfetamine	< 500 (negativo)	ng/mL	3		Metamfetamine, MDMA ed analoghi	
U-Cannabinoidi	< 50 (negativo)		3		THC	
U-Cocaina	< 300 (negativo)		3			
U-Metadone	< 300 (negativo)		3			
U-Oppiacei	< 300 (negativo)		3			

VALORI DI RIFERIMENTO DEGLI ESAMI DI LABORATORIO

Laboratorio di Analisi Chimico-cliniche - Cisanello

LIQUIDI BIOLOGICI VARI

esame	valore di riferimento	Tempi di risposta	unità di misura	note
Esame Liquido Ascitico				
Aspetto				
pH				
Peso specifico				
Proteine			g/dL	
Amilasi			U/L	
Leucociti totali			x10^3/µL	
- polinucleati			%	
- mononucleati			%	
Esame liquido Pleurico				
Aspetto				
pH				
Peso specifico				
Proteine			g/dl	
LDH			U/L	
Leucociti totali			x10^3/µL	
- polinucleati			%	
- mononucleati			%	

esame	valore di riferimento	Tempi di risposta	unità di misura	note
Esame Liquor cefalo rachidiano Aspetto Proteine totali Glucosio Cloro Leucociti totali	 15 - 45 60 - 80 113 - 131 0 - 5		 mg/dl mg/dL mEq/L µL	
Ricerca di IgG Anti Borrelia b. (su LIQUOR)	negativo	**5**		28
Ricerca Sangue occulto	< 40: negativo	**3**	µg/L	16 13

esame	valore di riferimento		Tempi di risposta	unità di misura	note
Studio morfologico delle emazie urinarie: ricerca acantociti	EMATURIA ISOMORFICA	• Ematurie isomorfiche > 80% • Assenza di acantociti • Assenza di cilindri	**5**	%	26
	EMATURIA DISMORFICA	• Emazie dismorfiche > 80% • Acantociti ≥ 5% • Emazie dismorfiche > 40% e/o Acanticiti ≥ 50% e/o cilindri ematici			
	EMATURIA DI TIPO MISTO	• Ematurie isomorfiche e dismorfiche in proporzioni diverse (Isomorfiche < 80%, dismorfiche > 20%), senza acantociti o cilindri ematici			

TABELLA DELLE METODICHE E DELLA PRECISIONE ANALITICA (CV%)

Laboratorio di Analisi Chimico-cliniche - Cisanello

LEGENDA: S=siero, P=plasma, SI=sangue intero, F=feci, U=urine

esame	metodica utilizzata	CV % ≤
P-ACE	Enzimatico-idrolisi substrato, Roche/Cobas C-501	6.16
P-Acidi bliari	Enzimatico-colorimetrica, Roche/Cobas C-501	5.26
P-Acido urico	Enzimatico-colorimetrica-uricasi, Roche/Cobas C-501	1.39
U-Acido urico	Enzimatico-colorimetrica-uricasi, Roche/Cobas C-501	1.37
S-Agglutinine a freddo	Emoagglutinazione, Metodo Manuale	-
P-Aggregazione piastrinica	Viscosimetrica, Medical System/Aggrecorder Chronolog	-
P-Albumina	Colorimetrica (BCG), Roche/Cobas C-501	2.05
P-Aldolasi	Cinetica Enzimatica, Roche/ Cobas C-501	1.47
S- α 1 antitripsina	Immunonefelometrica, Siemens /BNA II	4.4
S- α 1 glicoproteina acida	Immunoturbidimetrica Roche/Cobas C-501	2.83
S- AFP	Elettrochemiluminescenza, Roche /Cobas E-601	2.91
P-Amilasi	Enzimatico-colorimetrico-EPS, Roche/Cobas C-501	1.09
P-Amilasi pancreatica	Enzimatico-colorimetrica-EPS, Roche/Cobas C-501	1.29
U-Amilasi	Enzimatico-colorimetrica-EPS, Roche/Cobas C-501	0.98
S-Ammonio	Enzimatico-colorimetrico, Roche/Cobas C-501	4.71

esame	metodica utilizzata	CV % ≤
S-Anti Beta 2 glicoproteina	Immunoenzimatica, Orgentec/manuale	7.0
Antigene (Ricerca di) H. pylori nelle feci	Immunoenzimatica, Meridian/Manuale	-
S-Anti fosfolipidi - LAC	Immunoenzimatica, Orgentec/manuale	-
P-Antiplasmina	Cromogenica, I.L./TOP	10.0
S-Anti Protrombina	Immunoenzimatica, Orgentec/Manuale	7,0
S-Antistreptolisina O	Immunonefelometrica, Siemens/ BNA II	5.9
P-Antitrombina III°	Cromogenica anti X , IL/TOP	8,0
P- Apixaban dosaggio antiXa	Cromogenica, I.L./TOP	6.0
S-Apolipoproteina A1	Immunonefelometrica, Siemens /BNA II	5.6
S-Apolipoproteina B	Immunonefelometrica, Siemens/ BNA II	6.2
S-Aptoglobina	Immunoturbidimetrica, Roche/Cobas C-501	1.38
S-IgG anti Bartonella henselae e quintana, IgG, IgM	Immunofluorescenza/Vircell/Manuale	
S-β2 microglobulina	Immunonefelometrica, Siemens / BNA II	4.5
S-β HCG (per espianto)	Elettrochemiluminescenza, Roche /Cobas E-601	3.92
P-Bicarbonati	Enzimatico colorimetrico, Roche/Cobas C-501	2.07
P-Bilirubina diretta	Colorimetrica, Roche/Cobas C-501	1.77
P-Bilirubina totale	Colorimetrica DPD, Roche/Cobas C-501	1.86
S-Anti Bordetella pertussis	Immunoenzimatica, Technogenetics/DSX	3.1
S-Anti Borrelia	Immunoenzimatica, Technogenetics/DSX	1.2
Anti Borrelia IgG (su liquor)	Immunoenzimatica - ELFA/Biomerieux/Vidas	4,0
S-Anti Borrelia WB	Immunoblot, Siemens / Innolia	
P-BNP	Chemiluminescenza (CMIA), Abbott / Architect Ci4100	4,0
P-ProBNP	Elettrochemiluminescenza, Roche/Cobas E-601	3.37
S-CA 19.9	Elettrochemiluminescenza, Roche/Cobas E-601	3.98

esame	metodica utilizzata	CV % ≤
S-CA 125	Elettrochemiluminescenza, Roche/Cobas E-601	4.2
S-CA 15.3	Elettrochemiluminescenza, Roche/Cobas E-601	3.57
S-CA 72.4	Elettrochemiluminescenza, Roche/Cobas E-601	-
P-Calcio	Colorimetrica con NM-BAPTA, Roche/Cobas C-501	1.05
U-Calcio	Colorimetrica con NM-BAPTA, Roche/Cobas E-601	1.31
S-Catene leggere κ	Immunonefelometrica, Siemens / BNA II	4.2
S-Catene leggere λ	Immunonefelometrica, Siemens / BNA II	5.1
U-Catene leggere κ	Immunonefelometrica, Siemens / BNA II	2.7
U-Catene leggere λ	Immunonefelometrica, Siemens / BNA II	5.2
S-CEA	Elettrochemiluminescenza, Roche/Cobas E-601	2.9
S-Ceruloplasmina	Immunonefelometrica, Siemens / BNA II	3.2
S-Cystatina C	Immunonefelometrica Siemens/BNA II	5.8
S-Anticorpi anti-Citomeg. IgM	Chemiluminescenza (CMIA), Abbott/Architect	6.0
S-Anticorpi anti-Citomeg. IgG	Chemiluminescenza (CMIA), Abbott/Architect	5.0
S-Anti Chlamidia pneumoniae e Trachomatis (IgG, IgM)	Immunoenzimatica, Technogenetics/DSX	4.4
P-CK	Enzimatica colorimetrico, Roche/Cobas C-501	1.02
P-CK-MB in massa	Enzimatica colorimetrico con immunoinibizione, Roche/Cobas E-601	1.87
P-Cloro	Potenziometrico, Roche/Cobas C-501	1.52
U-Cloro	Potenziometrico, Roche/Cobas C-501	1.51
P-Colesterolo	Enzimatico colorimetrico, Roche/Cobas-501	2.33
P-Colesterolo HDL	Enzimatico colorimetrico, Roche/Cobas-501	1.75
P-Colesterolo LDL	Enzimatico colorimetrico, Roche/Cobas-501	1.32
P-Colinesterasi	Enzimatico colorimetrico, Roche/Cobas-501	0.96
S-Anti Coxiella	Immunoenzimatica, Technogenetics/DSX	1.7

esame	metodica utilizzata	CV %
S-Complemento C3c	Immunonefelometrica, Siemens / BNA II	5.1
S-Complementto C4	Immunonefelometrica, Siemens / BNA II	3.2
P-Complesso trombina-antitrombina	Immunoenzimatica, Siemens/ Manuale	7,0
P-Creatinina	Colorimetrico con picrato, Roche/Cobas C-501	2.43
U-Creatinina	Colorimetrico con picrato, Roche/Cobas C-501	1.40
S-Crioglobuline	Crioprecipitazione, Metodo Manuale	-
S-Curva glicemica	Enzimatico colorimetrica UV, Roche/Cobas C-501	-
S-Cy-fra 21.1	Elettrochemiluminescenza, Roche/Cobas E-601	-
P- Dabigatran dosaggio ECA	Cromogenica, Stago/ STA COMPACT	5.2
P- Dabigatran dosaggio dTT	Coagulativa, IL WERFEN/ACL TOP	6.0
P-Dimero D P-Dimero D (conferma)	Immunoturbidimetrica, IL/TOP Immunoenzimatica, Biomerieux / Vidas	3.2 0,1
S-Anti EBV VCAIgG, VCAIgM, EBNA, EA IgG	Chemioluminescenza Technogenetics/TGS TA	5.3
S-Elettroforesi proteica - Albumina - Alfa 1 - Alfa 2 - Beta 1 - Beta 2 - Gamma	Capillare, Sebia/Hydrasis	- 0.79 5.04 2.29 3.02 4.06 1.69
Emocromo con formula: - leucociti - eritrociti - emoglobina - piastrine	Citometrica a flusso- metodo scatter ottico, impedenziometrico, Dasit/XE-2100	 2.0 0.7 0.9 1.9
S-Anti Entamoeba	Immunoenzimatica, Technogenetics/DSX	5.1
P-Anticorpi anti eparina / PF4 - HIT	Immunoturbidimetrica, I.L./TOP	10.0

esame	metodica utilizzata	CV %
P-Eparina dosaggio/Attività antiXa	Cromogenica, I.L./TOP	5.0
Esame standard delle Urine	Spettrofotometrica, Menarini/Aution Max	-
Esame del sedimento urinario	Rilevatore di immagini, Beckman /Iris IQ 200 sprint	-
Valutazione morfologica delle emazie urinarie	Microscopia in contrasto di fase	
P-Fattore Vc	Coagulativa, I.L./TOP	11.0
P-Fattore VIIIc	Coagulativa, I.L./TOP	10.0
P-Fattore di crescita placentare	Elettrochemiluminescenza, Roche /Cobas E-601	2.53
P-SFLT-1	Elettrochemiluminescenza, Roche /Cobas E-601	2.67
S-Fattore reumatoide	Immunonefelometrica, Siemens/BNA II	6.2
S-Ferritina	Chemiluminescenza, Roche/E-601	2.67
P-Ferro	Colorimetrico con ferrozina,Roche/Cobas C-501	1.62
P-Fibrinogeno Clauss	Coagulativa, I.L./TOP	5.6
P-Fibrinogeno PT derivato	Coagulativa, I.L./TOP	3.5
S-Folato	Elettrochemiluminescenza, Roche/Cobas E-601	4.2
P-Fosfatasi alcalina	Enzimatico colorimetrica, Roche/Cobas C-501	2.43
P-Fosforo	Colorimetrico con molibdato UV, Roche/Cobas C-501	1.44
U-Fosforo	Colorimetrico con molibdato UV, Roche/Cobas C-501	1.50
P-Frammento protrombinico 1 + 2	Immunometrica, Dade-Behring/Manuale	7.75
S-Fruttosamina	Colorimetrico con Nitro Blu Tetrazolio, Roche/Cobas c-501	1.39
S-FTA	Immunofluorescenza/Bioscientifica/Manuale	-
P-γ-GT	Enzimatico colorimetrica, Roche/Cobas C-501	0.98
Glicosuria frazionata	Enzimatico colorimetrico UV, Roche/Cobas C-501	-
P-Glucosio	Enzimatico colorimetrico UV, Roche/Cobas C-501	1.49
U-Glucosio	Enzimatico colorimetrico UV, Roche/Cobas C-501	1.46
SI-HBA1C (Emoglobina glicata)	HPLC, Tosoh/G8	1.79
S-He4	Chemioluminescenza, Abbott/Architect	-

esame	metodica utilizzata	CV % ≤
S-Anticorpi anti HIV 1-2	Chemioluminescenza, Abbott/Architect	4.7
S-Anticorpi anti HIV 1-2	Immunoenzimatica con lettura a fluorescenza (ELFA), Biomerieux/Vidas	7.0
S-HTLV I-II	Chemioluminescenza, Abbott/Architect	4.4
S-IgG	Immunonefelometrica, Siemens/ BNA II	4.2
S-IgA	Immunonefelometrica, Siemens / BNA II	5.9
S-IgM	Immunonefelometrica, Siemens / BNA II	3.9
S-IgE totali	Immunonefelometrica, Siemens/ BNA II	3.8
Immunofissazione sierica e urinaria	Immunoelettroforetica, Sebia/Hydrasys	-
P-Lattato	Enzimatico colorimetrica, Roche/Cobas C-501	1.24
S-Anti Legionella	Immunoenzimatica, Technogenetics/DSX	2.3
S-Anti Leishmania	Immunoenzimatica, Technogenetics/DSX	0.5
S-Anti Leptospira	Immunofluorescenza, Daltec/Manuale	-
P-LDH	Enzimatico colorimetrica, Roche/Cobas C-501	0.96
P-Lipasi	Enzimatico colorimetrica, Roche/Cobas C-501	1.75
S-Lipoproteina a	Immunonefelometrica, Siemens/ BNA II	5.4
S-LAC Screening fosfolipidi (IgG, IgM)	Immunoenzimatica, Technogenetics/DSX	
P-Lupus anticoagulant (ricerca di, screening) P-Lupus anticoagulant veleno di vipera Russel (dRWT) P-Lupus anticoagulant dRVVT + fosfolipidi P-Lupus anticoagulant – Silica Clotting time	Coagulativa, IL/ TOP Coagulativa, IL/ TOP Coagulativa (silica clotting time), IL/ TOP Coagulativa (silica clotting time), IL/ TOP	6.0
S- Ab totali Anti Listeria monocytogenes	Immunofluorescenza/Euroimmun/Manuale	
P-Magnesio	Colorimetrico con Blu di Xilidile, Roche/Cobas C-501	1.01
U-Magnesio	Colorimetrico con Blu di Xilidile, Roche/Cobas C-501	2.83

esame	metodica utilizzata	CV % ≤
S-Markers Epatite A (Ig totali)	Chemioluminescenza potenziata, Ortho C.D./Vitros 3600	5.8
S-Markers Epatite A (IgM)		13.0
S-Markers Epatite B	Chemioluminescenza, Abbott/Architect	
S-HBsAg qualitativo		6.8
S-HBsAg quantitativo		4.4
S-AntiHBs		6.0
S-HBeAg		4.5
S-Anti HBe		4.0
S-Anti Core Ig totali		9.0
S-Anti Core IgM		6.5
S-Anti HCV Core Ag	Chemioluminescenza, Abbott/Architect	7.5
S-Anti HCV (Ig totali)	Chemioluminescenza potenziata, Ortho C.D./Vitros 3600	3.0
S-Anti HCV IgM	Immunoenzimatica colorimetrica, Technogenetics / DSX	4.5
S-Anti HCV (Test di conferma)	Immunoblot, Siemens / Innolia	
S-Markers Epatite D (Ig totali)	Immunoenzimatica colorimetrica, Technogenetics / DSX	4.1
S-Markers Epatite D (IgM)	Immunoenzimatica colorimetrica, Technogenetics / DSX	2.1
S-Ac anti -Mycoplasma pn.	Immunoenzimatica, Technogenetics / DSX	3,3
U-Microalbumina	Colorimetrico BCG, Roche/ Cobas C-501	1.78
P-Mioglobina	Immunoturbidimetrica Tina q., Roche / Cobas E-601	1.75
S-Monotest	Agglutinazione al lattice, Mascia Brunelli/Manuale	-
S-NSE	Elettrochemiluminescenza, Roche/Cobas E-601	-
S-Omocisteina	Immunoturbidimetrica, I.L./TOP	10.0
S-Osmolalità	calcolata	-
U-Osmolalità	calcolata	-
SI-Piruvato chinasi	pHmetria, Eurochem/CL 10 micro	-

esame	metodica utilizzata	CV % ≤
P-Plasminogeno	Cromogenica, I.L./TOP	8.0
P-Plasminogeno, inibitore 1 dell'attivatore, dos. antigenico	Immunoenzimatica/Technogenetics/DSX	6.0
P-Plasminogeno, inibitore 1 dell'attivatore, dos. attività	Immunoenzimatica, Technogenetics/DSX	6.0
P-Plasminogeno, attivatore tissutale, dosaggio antigenico	Immunoenzimatica, Technogenetics/DSX	6.0
P-Potassio	Potenziometrica indiretta, Roche/Cobas C-501	0.9
U-Potassio	Potenziometrica indiretta, Roche/Cobas C-501	0.94
S- Procalcitonina	Elettrochemiluminescenza, Roche /Cobas E-601	3.51
P-Proteina C (resistenza alla)	Coagulativa, I.L./TOP Coagulativa, I.L./TOP	8.0
P-Proteina C	Cromogenica, I.L./TOP	6.0
P-Proteina S libera quantitativa	Immunoturbidimetrica, I.L./TOP	6.0
S-Proteina C reattiva	Immunoturbidimetrica, Roche/Cobas C-501	1.57
S-Proteina C reattiva sensibile	Immunonefelometria, Dade/ BNA II	3.4
P-Proteine totali	Colorimetrico Biureto, Roche/Cobas C-501	1.32
U-Proteine totali	Colorimetrico Biureto, Roche/Cobas C-501	1.83
S-PSA	Elettrochemiluminescenza, Roche /Cobas E-601	3.0
S-PSA libero	Elettrochemiluminescenza, Roche /Cobas E-601	1.95
S-Reazione di Weil-Felix	Agglutinazione, Sclavo/Manuale	-

esame	metodica utilizzata	CV % ≤
SI-Resist. globulare osmotica	Colorimetrica, Metodo Manuale	-
SI-Reticolociti	Citometrica a flusso - Scatter Ottico in Oxazina, Siemens- Advia e Dasit-XE2100	12.5
S-Anti Rickettsia	Immunoenzimatica, Technogenetics/DSX	0.8
S-Anti Rickettsia tiphy	Immunofluorescenza, Daltec/Manuale	-
P-Rivaroxaban dosaggio anti Xa	Cromogenica, IL WERFEN/ACL TOP	3,0
S-Anticorpi anti-Rosolia IgM dosaggio	Chemiluminescenza, Roche/Cobas E-601	4.0
S-Anticorpi anti-Rosolia IgG	Chemiluminescenza, Roche/Cobas E-601	5.0
S-pS100	Elettrochemiluminescenza, Roche /Cobas E-601	-
F-Sangue occulto	Turbidimetrico, Medical Systems/OC Sensor	-
S-SCC	Chemioluminescenza, Abbott/Architect	-
S-Sieroamiloide A	Immunonefelometrica Siemens/BNA II	9.7
Sierodiagnosi Widal-Wright	Agglutinazione, Masciabrunelli/Manuale	-
S-Sifilide (Screening)	Chemiluminescenza, Abbott/Architect	4.4
S- Sifilide (Test di conferma) IgG	Immunoenzimatica, Technogenetics/DSX	7.2
S- Sifilide (Test di conferma) IgM	Immunoenzimatica, Technogenetics/DSX	1.9
P-Sodio	Potenziometrica indiretta, Roche/Cobas C-501	0.92
U-Sodio	Potenziometrica indiretta, Roche/Cobas C-501	1.31
P-aPTT	Coagulativa, I.L./TOP	2.0
P-Tempo di protrombina/I.N.R.	Coagulativa, I.L./TOP	3.0
P-Tempo Trombina	Coagulativa, I.L./TOP	8.0
Test di gravidanza (urine)	Immunologica Colorimetrica, Instalert Innovacon/Manuale	-
S-Anticorpi anti tossina tetanica	Immunoenzimatica, Technogenetics/DSX	-
S-Anticorpi anti-Toxoplasma IgM	Chemiluminescenza, Roche/Cobas E-601	3.0
S-Anticorpi anti-Toxoplasma IgM	Immunoenzimatica con lettura a fluorescenza (ELFA), Biomerieux/Vidas	4.2
S-Anticorpi anti-Toxoplasma IgG	Chemiluminescenza, Roche/Cobas E-601	4.0

esame	metodica utilizzata	CV % ≤
S-TPHA	Emoagglutinazione passiva/Mascia Brunelli/Manuale	
P-Transaminasi GO	Enzimatica-colorimetrica, Roche/Cobas C-501	1.77
P-Transaminasi GP	Enzimatica-colorimetrica, Roche/Cobas C-501	1.42
S-Transferrina	Immunoturbidimetrica, Roche/Cobas C-501	2.12
S-Transferrina (recettori solubili)	Immunonefelometrica, Siemens/BNA II	4.8
S-Transferrina desialata - 5 Sialo- - 4 Sialo- - 3 Sialo- - CDT	Capillare, Sebia/Hydrasis	- 2.33 0.50 2.45 6.45
P-Trigliceridi	Enzimatica Colorimetrica, Roche/Cobas C-501	1.49
S-Anticorpi anti-tripanosoma cruzii	Chemiluminescenza, Abbott/Architect	-
P-Troponina T HS	Chemiluminescenza, Roche/Cobas E-601	3.03
P-Urea	Enzimatica-colorimetrica Ureasi, Roche/Cobas C-501	1.64
U-Urea	Enzimatica-colorimetrica Ureasi, Roche/Cobas C-501	1.84
VES	Microfotometro Capillare, TEST 1/Alifax	-
S-Vitamina B12	Chemiluminescenza, Roche/Cobas E-601	2.69
S-B12 Attiva (Holo-TC)	Chemiluminescenza, Abbott/Architect	

Nota alla tabella:

I dati relativi ai CV % vengono revisionati a cura dei Responsabili di settore, annualmente, sulla base dei dati dell'ultimo mese, dei CQI, per il range più vicino alla normalità.

TABELLA DELLE METODICHE (FARMACI E DROGHE)

Laboratorio di Analisi Chimico-cliniche - Cisanello
LEGENDA: S=siero, P=plasma, SI=sangue intero, F=feci, U=urine

esame	metodica utilizzata	CV % ≤
P/-Acido valproico	Chemiluminescenza, Abbott/Architect	7.39
P/U-Barbiturici	Immunoenzimatico omogeneo, Abbott / Architect Ci-4100	-
U-Benzodiazepine	Immunoenzimatico omogeneo, Abbott / Architect Ci-4100	-
P-Carbamazepina	Chemiluminescenza, Abbott/Architect	8.5
P-Digossina	Immunoturbidimetrica kims, Roche/Cobas C-501	4.93
P-Etanolo	Enzimatico colorimetrico, Roche/Cobas C-501	2.87
P-Fenitoina	Chemiluminescenza, Abbott/Architect	8.4
P-Fenobarbital	Chemiluminescenza, Abbott/Architect	8.4
S-Litio	Colorimetrico, Roche/Cobas C-501	3.06
P-Paracetamolo	Immunoenzimatico omogeneo, Abbott / Architect Ci-4100	3.23
P-Salicilati	Colorimetrico, Roche / Cobas C-501	1.20
P-Teofillina	Immunoturbidimetrica kims, Roche/Cobas C-501	3.63
P/U-Triciclici	Immunoenzimatico omogeneo, Abbott / Architect Ci-4100	2.1
S-Vancomicina	Chemiluminescenza, Abbott/Architect	5.9

Laboratorio di Analisi Chimico-cliniche - Cisanello
LEGENDA: S=siero, P=plasma, SI=sangue intero, F=feci, U=urine

esame	metodica utilizzata	CV % ≤
U-Amfetamine	Immunoenzimatico omogeneo, Abbott / Architect Ci-4100	-
U- Cannabinoidi	Immunoenzimatico omogeneo, Abbott / Architect Ci-4100	-
U- Cocaina	Immunoenzimatico omogeneo, Abbott / Architect Ci-4100	-
U-Metadone	Immunoenzimatico omogeneo, Abbott / Architect Ci-4100	-

U-Oppiacei	Immunoenzimatico omogeneo, Abbott / Architect Ci-4100	-

NOTE ESPLICATIVE PER LA RACCOLTA E L'INVIO DEI CAMPIONI

1 - La provetta contiene l'anticoagulante EDTA tripotassico. Dopo il prelievo mescolare bene, lentamente, per inversione.

2 - La provetta contiene l'anticoagulante CITRATO di SODIO. Dopo il prelievo mescolare bene, lentamente, per inversione; la provetta va riempita (TASSATIVAMENTE!) fino al livello predeterminato o al segno di riferimento.

4 - La provetta contiene un ANTIGLICOLITICO (Fluoruro di sodio e ossalato di potassio). Dopo il prelievo mescolare bene, lentamente. per inversione.

5 - Il prelievo deve essere inviato IMMEDIATAMENTE in Laboratorio, in BUSTA SEPARATA e deve essere indicata l'ora sulla provetta.

6 - Esame da eseguire sulla raccolta delle urine delle 24 ore: scartare la prima minzione del mattino (per es. ore 07) e raccogliere l'urina fino alla prima minzione del giorno successivo compresa (ore 07). Mescolare bene il contenuto del recipiente di raccolta e versare una aliquota in provetta. Riportare la diuresi totale in mL sulla provetta e sulla scheda di richiesta.

7 - Inviare nella medesima richiesta sia il prelievo di sangue che il campione di urina; per il calcolo della Clearance della Creatinina o dell'Urea indicare sempre la DIURESI totale in mL e l'intervallo di raccolta.

8 - Non stappare la provetta.

9 - Usare una sola scheda di richiesta per il test.

10 - Precisare i tempi di prelievo/raccolta se diversi da quelli standardizzati (cfr. tabella dei valori di riferimento).

11 - Glucosio post-prandiale: va effettuato un prelievo due ore dopo l'inizio del pasto.

Rev.28 (il Direttore / i Responsabili di Settore)

12 - Test da carico orale di 50 g di glucosio e misurazione della glicemia dopo 1 ora.

13 - <u>Istruzioni per l'invio del campione.</u>
- **a) Togliere il tappo del flaconcino di raccolta.**
- **b) Immergere l'asticella collegata al tappo in vari punti del materiale fecale, prelevandone una parte.**
- **c) Riavvitare il tappo ed inviare al Laboratorio (nell'attesa conservare in luogo fresco).**
- **d) Non è necessaria l'esclusione di alcun alimento dalla dieta.**

16 – Inviare il campione nell'apposito contenitore.

19 - Il prelievo deve essere inviato IMMEDIATAMENTE in Laboratorio, NELL'APPOSITO CONTENITORE REFRIGERATO

20 – Nel caso in cui è richiesta SOLO la VES segnalarlo nell'apposito spazio dell'etichetta barcode

22- Per campioni con piastrinopenia inviare provetta con tappo lilla (da emocromo) e celeste (da coagulazione) in busta separata e segnalarlo al laboratorio

23-Deve essere inviato in regime di urgenza con scheda separata

24-Si esegue solo su appuntamento (tel. 5645)

25-Segnalare in maniera evidente sulla provetta che si tratta del dosaggio di etanolo

26-Il prelievo si esegue su appuntamento. La raccolta dei campioni deve essere eseguita in Laboratorio.

27-per il dosaggio di questi analiti è necessario allegare anche le notizie cliniche – scheda specifica

28- Occorre l'invio contemporaneo di un campione di siero e di liquor per il dosaggio di albumina sierica e su liquor.

ALTRE NOTE ESPLICATIVE

a) Il Dimero D costituisce un frammento di degradazione della fibrina ad opera della plasmina. Tale test ha in larga parte sostituito il dosaggio dei frammenti di degradazione del fibrinogeno (FDP o PDF).

b) Non è indicato l'intervallo terapeutico, poiché la dose viene stabilita dal medico curante.

c) Il test di conferma viene eseguito sui risultati con valore di poco superiore al CUT-OFF del metodo di screening, per quanto riguarda i pazienti ricoverati. Per i pazienti esterni, il test di conferma viene eseguito solo su richiesta del medico curante.

d) Risultato calcolato. Per il calcolo è necessaria l'esecuzione dei seguenti esami: S-Creatinina, U-Creatinina, Volume urinario in mL delle 24 ore.

e) Risultato calcolato. Per il calcolo è necessaria l'esecuzione dei seguenti esami: S-Urea, U-Urea, Volume urinario in mL delle 24 ore.

f) Il metodo ELFA su Vidas per il dosaggio del Dimero-D viene eseguito su richiesta specifica

g) Inviare il campione prelevato a 4 ore dalla somministrazione di EBPM (Eparina a basso peso molecolare) con consegna immediata

AZIENDA OSPEDALIERO-UNIVERSITARIA PISANA
Dipartimento ad Attività Integrata Medicina di Laboratorio
Direttore Prof. Romano Danesi
S. D. Laboratorio Chimica e Endocrinologia
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Pisa, 30/05/2018

CERTIFICAZIONE DI QUALITA'

La sottoscritta Sessa Maria Rita, in qualità di Direttore del Laboratorio Chimica e Endocrinologia, certifica sotto la propria responsabilità quanto segue:

- il Laboratorio partecipa al Controllo di Qualità Nazionale **DicoCARE VEQ;**
- il Laboratorio partecipa al Controllo di qualità Europeo **EQAS – IFC;**
- il Laboratorio partecipa al Controllo di Qualità ufficialmente adottato dalla **Regione Toscana,** risultando all'interno del range di qualità nei parametri testati;
- il Laboratorio partecipa al Controllo di Qualità Europeo **DEQAS, UK**
- il Laboratorio esegue un controllo di qualità giornaliero, refertando dati solo se i controlli sono all'interno del range di accettabilità (regole di Westgard);
- il Laboratorio sta seguendo i percorsi di **Accreditamento e Certificazione** predisposti dalla Regione Toscana, risultando in linea con gli stessi;
- la documentazione dei risultati dei controlli di qualità, secondo quanto disposto dalle norme di accreditamento di cui sopra, è sempre visionabile nel Laboratorio;
- la documentazione dello stato del percorso di accreditamento è visionabile presso la Direzione Sanitaria dell'Azienda Ospedaliero-Universitaria Pisana. I percorsi validati sono visionabili sul sito INTRANET nella sezione Qualità e Accreditamento.

Rilascio la presente dichiarazione per tutti gli scopi consentiti dalla legge.

In fede

Dr. Maria Rita Sessa

AZIENDA OSPEDALIERO - UNIVERSITARIA PISANA
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N. screening: 025

Esame: rT3
Valori di riferimento: <0,7 ng/ml

Referto completato: 29/05/2019

Data	TEMPO	Risultato (ng/ml)
18/3/2019	Basale	0,19
18/3/2019	5 h	0,21
19/3/2019	Day 1	0,16
1/4/2019	Day 14	0,16
15/4/2019	Day 28	0,22
29/4/2019	Day 42	0,22

Il Dirigente
D.ssa Maria Rita Sessa

AZIENDA OSPEDALIERO - UNIVERSITARIA PISANA
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31/05/19

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Dipartimento di Medicina di Laboratorio
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Tel. 050-995012 - Fax. 050-995025

CFCSF (STUDIO SOMAGEL)

Referto completato: 16/04/2019 16:26

Richiesta n° **25/039417**
Data Accettazione: 16/04/2019 12:09:04
Sig.ra [redacted]

Note: DAY 42

Data di Nascita:16/11/1988

Esame	*Metodo*	*Esito*	*Unità di misura*	*Valori di riferimento*	*Materiale*
T.S.H.	*ICMA*	2,170	mUI/L	0,400 - 4,000 WHO 2nd IRP 80/558	*siero*
fT3	*CLIA*	3,90	ng/L	2,70 - 5,70	*siero*
fT4	*CLIA*	1,07	ng/dL	0,70 - 1,70	*siero*

Il Dirigente
ROBERTA CENTONI
(Certificato n° 29E3531A9C6B2A3DA6D1BC994E9F3B46)

Referto firmato elettronicamente secondo le norme vigenti: Legge 15 marzo 1997, n. 59; D.P.R. 10 novembre 1997, n.513; D.P.C.M. 8 febbraio 1999; D.P.R 8 dicembre 2000, n.445; D.L. 23 gennaio 2002, n.10

16 APPENDICES

16.1 STUDY INFORMATION

16.1.11 Publications based on the study

NA

16 APPENDICES

16.1 STUDY INFORMATION

16.1.12 Important publications referenced in the report

NA

16 APPENDICES

16.2 PATIENT DATA LISTING

16.2.1 Discontinued patients

NA

16 APPENDICES

16.2 PATIENT DATA LISTING

16.2.2 Protocol deviations

Appendix 16.2.2 Protocol deviations

PatNo	First deviation	Second deviation	Classification	Safety	ITT	PP	POP
1	Incorrect laboratory procedure		**Minor**	YES	YES	YES	Safe, ITT, PP
2	Incorrect laboratory procedure	No treatment for forgetfulness on the 20th day	**Minor**	YES	YES	YES	Safe, ITT, PP
3	Screening 19 days out of range		**Minor**	YES	YES	YES	Safe, ITT, PP
4	**Screening failure**			**NO**	**NO**	**NO**	**SF**
5	Screening 17 days out of range	EoS vist out of range	**Minor**	YES	YES	YES	Safe, ITT, PP
6	Screening 18 days out of range		**Minor**	YES	YES	YES	Safe, ITT, PP
7	Screening 16 days out of range		**Minor**	YES	YES	YES	Safe, ITT, PP
8	**Withdrawal of informed consent**			**NO**	**NO**	**NO**	**SF**
9	Screening 24 days out of range		**Minor**	YES	YES	YES	Safe, ITT, PP
10	Screening 13 days out of range		**Minor**	YES	YES	YES	Safe, ITT, PP
11	Screening 13 days out of range		**Minor**	YES	YES	YES	Safe, ITT, PP
12	Screening 11 days out of range	Incorrect timing for returning the medication kit	**Minor**	YES	YES	YES	Safe, ITT, PP
13	Screening 19 days out of range		**Minor**	YES	YES	YES	Safe, ITT, PP
14	**Withdrawal of informed consent**			**NO**	**NO**	**NO**	**SF**
15	**Withdrawal of informed consent**			**NO**	**NO**	**NO**	**SF**
16	Screening 11 days out of range		**Minor**	YES	YES	YES	Safe, ITT, PP
17	Screening 9 days out of range		**Minor**	YES	YES	YES	Safe, ITT, PP
18	Screening 5 days out of range	No urea analysis at the screening	**Minor**	YES	YES	YES	Safe, ITT, PP
19				YES	YES	YES	Safe, ITT, PP
20	Screening 5 days out of range	SBP=94 at screening out of range	**Minor**	YES	YES	YES	Safe, ITT, PP
21				YES	YES	YES	Safe, ITT, PP
22				YES	YES	YES	Safe, ITT, PP
23	Incorrect timing for returning the medication kit		**Minor**	YES	YES	YES	Safe, ITT, PP
24	No treatment for forgetfulness on the 17th and 20th day		**Minor**	YES	YES	YES	Safe, ITT, PP
25				YES	YES	YES	Safe, ITT, PP
26	3rd control Day 14 out of range		**Minor**	YES	YES	YES	Safe, ITT, PP
27	No treatment for forgetfulness on the 19th day		**Minor**	YES	YES	YES	Safe, ITT, PP
28				YES	YES	YES	Safe, ITT, PP
29				YES	YES	YES	Safe, ITT, PP
30				YES	YES	YES	Safe, ITT, PP
31				YES	YES	YES	Safe, ITT, PP
32				YES	YES	YES	Safe, ITT, PP
33				YES	YES	YES	Safe, ITT, PP
34				YES	YES	YES	Safe, ITT, PP

16 APPENDICES

16.2 PATIENT DATA LISTING

16.2.3 Patients excluded from the efficacy analysis

NA

16 APPENDICES

16.2 PATIENT DATA LISTING

16.2.4 Demographic data

See Table 7

16 APPENDICES

16.2 PATIENT DATA LISTING

16.2.5 Compliance and -or drug concentration data

NA

16 APPENDICES

16.2 PATIENT DATA LISTING

16.2.6 Individual efficacy response data

NA

16 APPENDICES

16.2 PATIENT DATA LISTING

16.2.7 Adverse event listings

See Table 12

16 APPENDICES

16.2 PATIENT DATA LISTING

16.2.8. Listing of individual laboratory measurements by patient, when required by regulatory authorities

NA

16 APPENDICES

16.3 CASE REPORT FORMS

16.3.1 CRFs for deaths, other serious adverse events and withdrawals for AE

NA

16 APPENDICES

16.3 CASE REPORT FORMS

16.3.2 Other CRFs submitted

NA

16 APPENDICES

16.4. INDIVIDUAL PATIENT DATA LISTING (US ARCHIVIAL LISTING)

NA

ANNEX I

SYNOPSIS

See Appendix 16.1.1.

ANNEX II

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S) OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

See Appendix 16.1.5.

ANNEX III

STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

Timing of event		Screening	Baseline	Control 1	Control 2	Control 3	EOT	EOS
		Day -15 to Day 0	Day 0 (before dosing)	Day 0 +5 hours	Day 1 +24 hours	Day 14	Day 28	Day 42
Informed Consent		x						
Eligibility		x	x					
Demography & Lifestyle		x						
Medical History		x						
Haematology		x						x
Blood chemistry		x						x
Urine Drug Screening		x						
Urinalysis		x						x
Ioduria		x						x
Virology		x						
Alcohol/Nicotine Consumption		x						
TSH concentration[1]		x	x	x	x	x	x	x
Free T4, r-T3, T3[1]			x	x	x	x	x	x
Pregnancy Test		x	x					
Treatment[2]			x		x	x	x	x
Vital Sign (SBP, DBP, HR, RF, Temp)		x	x	x	x	x	x	x
Physical Examination		x	x					x
ECG		x						x
Adverse Events			x	x	x	x	x	x
Local Tolerability assessed	by investigators			x	x	x	x	x
	by subject (diary)			x	x	x	x	x

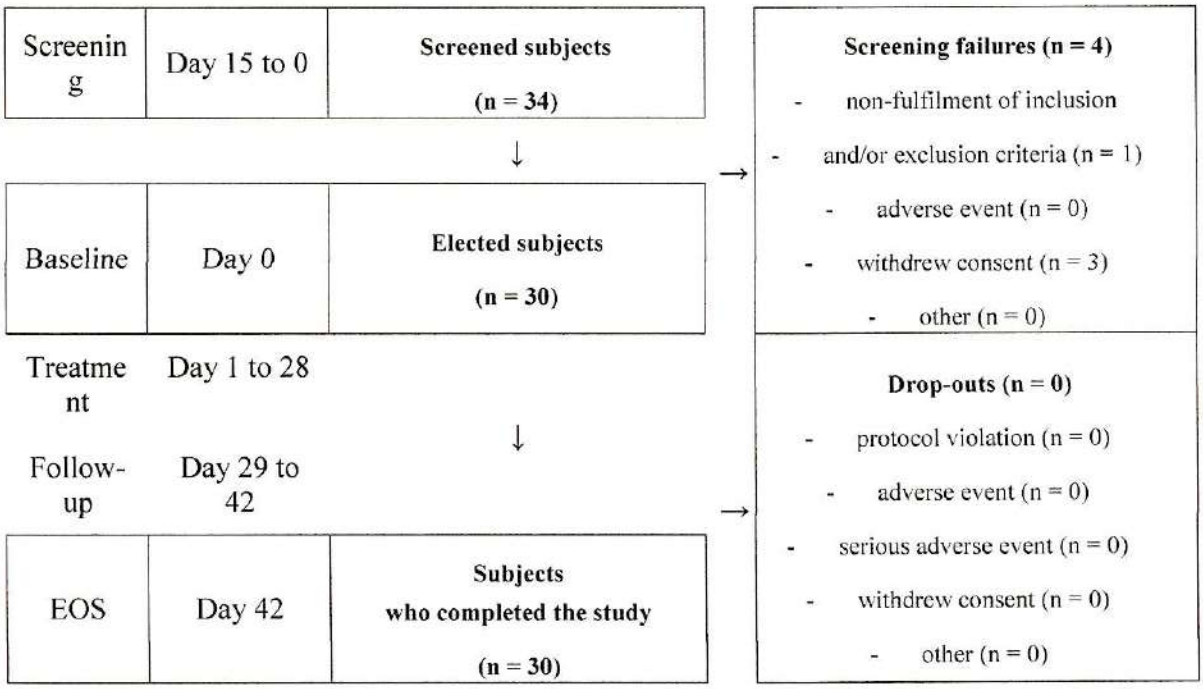
X[1]: T_4, rT_3, T_3 and TSH concentrations were evaluated at Baseline before dosing and 5 hours after dosing, at Day 1 (24 hours after dosing) , at Day 14, at Day 28 and Day 42

X[2]: the treatment was started after reconfirmation of eligibility criteria, a negative pregnancy test and plasma concentrations obtained. The treatment started on each thigh (10 grams) per day during the first two days, followed by 5 grams per thigh until the end of a 4-week period.

ANNEX IV

DISPOSITION OF PATIENTS

The following skeleton diagram that provides the number of subjects screened, screening failure, treated, dropped out or completed.



ANNEX V

LISTING OF PATIENTS WHO DISCONTINUED THERAPY

None.

ANNEX VI

LISTING OF PATIENTS AND OBSERVATIONS EXCLUDED FROM EFFICACY ANALYSIS

None.

ANNEX VII

LISTING OF PATIENTS EXCLUDEDE FROM EFFICACY ANALYSIS

None.

ANNEX VIII

GUIDANCE FOR SECTION 11.4.2 - STATISTICAL/ANALYTICAL ISSUES AND APPENDIX 16.1.9

None.