



INSTITUT BIOCHIMIQUE SA

# STATISTICAL ANALYSIS PLAN

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STUDY PROTOCOL N°13US-T404

Phase IV

An open-label therapeutic efficacy study of Tirosint® (levothyroxine sodium) capsules in thyroidectomized patients taking proton pump inhibitors.

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**SIGNATURES**

**Protocol number:** 13US-T404

**Title:** An open-label therapeutic efficacy study of Tirosint® (levothyroxine sodium) capsules in thyroidectomized patients taking proton pump inhibitors.

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## LIST OF ABBREVIATIONS

Abb.	Notes
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BOCF	Basal Observation Carried Forward
BP	Blood Pressure
BW	Body Weight
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CPK	Creatine Phosphokinase
CRF	Case Report Form
FT3	Free Triiodothyronine
FT4	Free Thyroxine
GERD	Gastroesophageal Reflux Disease
GMP	Good Manufacturing Practice
HDL-C	High-density Lipoprotein Cholesterol
HR	Heart Rate
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
ITT	Intention to treat
IU	International Unit
LDL-C	Low-density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
LT4	Levothyroxine
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to treat
MW	Molecular Weight
NIMP	Non-Investigational Medicinal Product
OTC	Over-The-Counter
PP	Per-Protocol
PPI	Proton Pump Inhibitor
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event

<b>Abb.</b>	<b>Notes</b>
R&D	Research and Development
Rx	Prescription drug
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SHBG	Sex-Hormone Binding Globulin
SOC	System Organ Class
SP	Safety Population
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-Emergent Adverse Event
TBG	Thyroxine-Binding Globulin
TC	Total Cholesterol
TFT	Thyroid Function Test
TG	Triglycerides
TSH	Thyroid Stimulating Hormone
TT3	Total Triiodothyronine
TT4	Total Thyroxine
VLDL-C	Very Low-density Lipoprotein Cholesterol
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
WIC	Written Informed Consent



## 1 INTRODUCTION

This document outlines the statistical methods to be implemented in the analysis of the data of IBSA 13US-T404 Clinical Trial. The purpose of this plan is to provide general guidelines from which the analysis will proceed, containing a more technical and detailed elaboration of the principal features of the analysis described in the protocol. Any changes to the protocol or CRF may necessitate updates to the SAP. In case of deviations from this updated statistical analysis plan, explanations will be provided in the statistical report.

## 2 VERSION HISTORY

Version Number	Summary/Reason for changes	Date Issued
<b>Draft 1.0</b>	Draft specification based on the Clinical Study Protocol (Version 6.0, 17 June 2019), CRF (Version 3.0 – 05 November 2018) and Patient’s Diary (Version 2.0 – 20 July 2018).	13/09/2021
<b>Draft 2.0</b>	Internal review. Added overall compliance tables and Daily dosage; Splitted the secondary efficacy endpoint models on laboratory data; Modified the mITT definition.	15/10/2021
<b>Draft 3.0</b>	Primary and secondary analysis will be repeated on original data. Added details on model covariance structure.	10/11/2021
<b>Final 1.0</b>	First final version release.	06/12/2021
<b>Final 2.0</b>	The baseline value covariates will not be included in the repeated measures models.	23/12/2021

### 3 STUDY OBJECTIVES HYPOTHESIS TESTING

#### 3.1 STUDY OBJECTIVES

The objective of this study is to evaluate the therapeutic efficacy of Tirosint® capsules in patients with a history of hypothyroidism and on proton pump inhibitors.

#### 3.2 HYPOTHESES TO BE TESTED

##### Primary objective

The primary objective of this study is to evaluate the therapeutic efficacy of Tirosint® capsules in patients with a history of hypothyroidism and on PPIs.

The hypothesis is that PPIs may have less of an effect on the absorption, as assessed by alteration in serum TSH, of Tirosint® capsules when compared to standard tablets therapy in this patients' population.

##### Secondary objective

The secondary objectives of this study are to evaluate any biochemical changes in creatine phosphokinase (CPK), sex hormone binding globulin (SHBG), ferritin, angiotensin converting enzyme (ACE) level, and lipid panel, as well as the change in daily LT4 dose in the same population upon switch from conventional tablets to Tirosint® capsules.

### 4 STUDY DESIGN

This was an open-label, phase IV study.

Enrolment was to be stopped as soon as 48 patients were completed or 60 patients included in the Tirosint treatment phase, whatever came first.

Adult patients with a history of hypothyroidism due to total thyroidectomy, who were on stable doses of levothyroxine tablets (between 88 and 250 mcg daily) for at least 6 weeks before screening visit and with a history of gastroesophageal reflux disease (GERD) or associated gastrointestinal issues on prescription (Rx) PPIs (i.e. omeprazole  $\geq$  20 mg daily, or esomeprazole  $\geq$  20 mg daily, or lansoprazole  $\geq$  15 mg daily, or dexlansoprazole  $\geq$  30 mg daily, or pantoprazole  $\geq$  40 mg daily, or rabeprazole  $\geq$  20 mg daily) for at least 8 weeks before screening visit were included in the study.

During the screening visit, subjects (holding their morning dose of LT4) underwent screening serum measurements for TFTs (TSH, FT4, free T3 [FT3], total T3 [TT3]), along with a physical examination. Subjects complying with inclusion/exclusion criteria entered a run-in period, in which they continued taking their levothyroxine and PPI medications as per prescription, at their current dose. Should the patient require LT4 dose adjustment at screening visit, it was possible to re-screen the patient until TSH normalization under the new dose.



Four to 6 weeks later (from screening or last re-screening), subjects (fasting and holding their morning dose of LT4) underwent baseline serum measurements of TSH, FT4, FT3, TT3, as well as total T4 (TT4), creatine phosphokinase (CPK), sex hormone binding globulin (SHBG), ferritin, angiotensin converting enzyme (ACE) level, and lipid panel (triglycerides [TG], total cholesterol [TC], high-density lipoproteins [HDL], low-density lipoprotein [LDL], and very-low-density lipoproteins [VLDL]) as baseline thyroid function related serum laboratory assessments. Patients were then switched to Tirosint® capsules at the same daily dose.

Patients were to remain on Tirosint® for 12 weeks (time frame allowed: 11-13 weeks) and were to continue their regular intake of Rx PPI, throughout the whole study duration, according to prescription. Halfway through the Tirosint® treatment period (time frame allowed: 5-7 weeks), subjects reported to the clinical center and (holding their morning dose of LT4) underwent intermediate serum measurements of TSH, FT4, FT3, TT3, for safety assessment.

At the end of the 12 week Tirosint® treatment period, patients were to report to the study site for the final visit and (fasting and holding their morning dose of LT4) they underwent a physical examination, and serum measurements of TSH, FT4, TT4, FT3, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel.

In addition to the laboratory tests, the subjects' safety was evaluated throughout the study by adverse event monitoring.

The study schedule is reported in the following table:

Visit	V1	V2	V3	V4
	Screening	Baseline	Interim	Final
Week	-4/-6	0	6±1	12±1
Period	Run-in		Treatment Period <sup>6</sup>	
Day	D-28/-42 <sup>7</sup>	D1	D42 (35-49)	D84 (77-91)
<b>Enrolment:</b>				
Informed Consent	X			
Demographic Data	X			
Medical and Medication History	X			
Physical Exam	X <sup>1</sup>	X <sup>2</sup>		X <sup>1</sup>
Thyroid function tests	X <sup>3</sup>			
Urine pregnancy test	X	X		
Inclusion/exclusion criteria	X	X		
Inclusion		X		
<b>Interventions:</b>				
Levothyroxine as prescribed				
Tirosint capsules				
PPI as prescribed				
Drug dispensing		X	X	

Drug return			X	X
<b>Outcomes:</b>				
Thyroid function tests		X <sup>4</sup>	X <sup>3</sup>	X <sup>4</sup>
Serum lab tests <sup>5</sup>		X		X
Pill count (compliance)			X	X
AEs and concomitant medications monitoring		X	X	X

<sup>1</sup> Vital signs, height (V1 only), weight, neck exam, cardiac exam, and respiratory exam

<sup>2</sup> Weight

<sup>3</sup> TSH, FT4, FT3 and TT3 (sample to be collected pre-dose) (same tests in case of re-screening)

<sup>4</sup> TSH, FT4, TT4, FT3 and TT3 (sample to be collected pre-dose)

<sup>5</sup> CPK, SHBG, ferritin, ACE level, and lipid panel (TC, LDL-C, HDL-C, VLDL-C, and TG) (sample to be collected pre-dose and in fasting conditions)

<sup>6</sup> Day 1 of treatment period was the first day of Tirosint® intake and should be the day of V2.

<sup>7</sup> In case re-screening is necessary, this time period may be extended, provided that time interval between re-screening and V2 is kept within -28/-42 days, and that the overall screening period does not exceed 4 months.



### *Changes from study protocol*

#### Treatment compliance

Study protocol states that treatment compliance will be evaluated separately over run-in and treatment periods. To have a more accurate compliance evaluation it will also be computed by visit both from the Study Diary and Drug accountability.

Compliance from the Drug accountability will be computed on the amount of drug to be taken among visits rather than on the number of capsules, as the number of capsules differs according to the prescribed dosages.

#### Analysis Sets

In order to assess sensitivity on efficacy analysis an additional analysis population will be defined. Modified Intention-To-Treat population will be defined as: all included patients who received at least one dose of the study medication and performed at least Visit 2 and Visit 3 laboratory assessments under the same LT4 dose with a valid TSH value.

#### Baseline covariates

Since the repeated measures analysis will be performed only on two time points (one baseline and one post baseline), the models will not include the basal value also as additional covariate for the analysis.

## **4.1 SAMPLE SIZE**

A sample size of 48 subjects had 70% power to detect a difference in means of TSH of 0.7, assuming a standard deviation of differences of 1.9, using a paired t-test with a 0.050 two-sided significance level. To account for a drop-out and dose adjustment rate of about 20%, a maximum number of 60 subjects were to be included in the study (Tirosint® treatment phase).

The study was early terminated with 47 patients included in the Tirosint ® treatment phase and 45 patients completed, due to the COVID-19 pandemic outbreak.

## **4.2 RANDOMISATION**

Not applicable. This is an open label non-randomized study.

## **5 DEFINITIONS AND DATA CONVENTIONS**

### Age

Age will be calculated in decimal form as portion of the date of screening visit minus the date of birth, divided by 365.25 days per year, and then rounded down, that is:

$$\text{Age (years)} = \text{Floor}((\text{date of screening visit} - \text{date of birth}) / 365.25).$$

Body Mass Index (BMI)

BMI will be computed using the following formula:

$$\text{BMI} = \text{Body Weight (kg)} / (\text{Height (m)})^2$$

Daily dosage

Daily dosage (mcg) will be computed for each patient as:

$$\text{Daily Dosage} = \left( \frac{\sum_{i=1}^7 (\text{daily dosage}_i [\text{mcg}])}{7} \right)$$

where “i” is the day of the week.

Daily dosage/Body Weight

Daily dosage/Body Weight (mcg / kg) will be computed for each patient as:

$$\text{Daily Dosage/Body Weight} = \frac{\left( \frac{\sum_{i=1}^7 (\text{daily dosage}_i [\text{mcg}])}{7} \right)}{\text{Weight [kg]}}$$

where “i” is the day of the week.

Prior medications

Medications reported with an end date before the first study treatment administration (end date < date of first study treatment administration). As prior medication will be also indicated all medications reported by patients who didn't took the study treatment.

Concomitant medications

Medications reported as ongoing or with an end date after the first study treatment administration (ongoing or end date ≥ date of first study treatment administration).

Treatment-Emergent Adverse Events (TEAEs)

Adverse events who started after the start of the study treatment, adverse events without start date and with an end date after the start of the study treatment or adverse events without start date reported as ongoing (for patients who take at least one dose of study treatment).

Pre-Treatment Adverse Events (PTAEs)

Adverse events started after the subject's inclusion into the study but before the effective study treatment period (start date < date of first study treatment administration).

Serious Adverse Events (SAEs)

Adverse Event judged as serious.

Drug related Adverse Events

Adverse Events with a relationship to treatment reported as "Certain", "Probable" or "Possible".

Adverse events leading to discontinuation

Adverse Events leading to discontinuation is an AE with action taken equal to "Drug withdrawn".

Adverse events leading to death

Adverse Events leading to death is an AE with outcome equal to "Fatal".



## **6 ANALYSIS SETS**

### **6.1 INTENTION-TO-TREAT POPULATION (ITT)/ FULL ANALYSIS SET (FAS)**

All included patients who received at least one dose of the study medication.

### **6.2 PER-PROTOCOL POPULATION (PP)**

All patients in the ITT population who completed the study and who did not have any major protocol violations (e.g. use of prohibited concomitant medications, violation of major inclusion/exclusion criteria).

### **6.3 SAFETY POPULATION (SP)**

All included patients.

### **6.4 OTHER ANALYSIS SET**

#### **MODIFIED INTENTION-TO-TREAT POPULATION (ITT)**

All included patients who received at least one dose of the study medication and performed at least Visit 2 and Visit 3 laboratory assessments under the same LT4 dose with a valid TSH value.

### **6.5 TREATMENT MISALLOCATIONS**

Not applicable.

### **6.6 PROTOCOL DEVIATIONS**

Any protocol violation or deviation (i.e., wrong inclusion, poor compliance, forbidden concomitant medications etc.) will be discussed by case before statistical analysis with the clinical team and described in the statistical report.

Violations will be classified as major violation or minor violation according to the impact on subject safety, the effect on completeness, accuracy and reliability of the data collected for the study, and the influence on the efficacy assessments. Protocol deviations related to COVID-19 will also be identified.



## 7 VARIABLES OF INTEREST

### 7.1 EFFICACY VARIABLES

#### 7.1.1 Primary efficacy variables

The primary efficacy variable is the serum levels of TSH.

Serum levels of TSH will be measured at screening visit(s), at baseline, halfway through the treatment period and at the final visit.

The serum levels of TSH recorded after changes in LT4 dose will not be considered for the analysis.

#### 7.1.2 Secondary efficacy variables

The secondary efficacy variables are the serum levels of FT4, TT4, FT3, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel; and the LT4 dose adjustment.

Serum levels of FT4, FT3 and TT3 will be measured at screening visit(s), at baseline, halfway through the treatment period and at the final visit. In addition, serum levels of TT4, CPK, SHBG, ferritin, ACE level, and lipid panel (TC, HDL-C, LDL-C, VLDL-C, TG) will be measured at baseline and at the end of the 12-week treatment period (Final visit).

The change in serum levels of TSH, FT4, FT3, TT3 at Visit 3 vs baseline will also be analysed as secondary efficacy endpoint.

The serum levels of TSH, FT4, TT4, FT3, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel recorded after changes in LT4 dose will not be considered for the analysis.

LT4 dose adjustment will be evaluated both in terms of number of patients requiring changes in daily dose during the treatment period and as mean change in daily LT4 dose at the end of the treatment period versus baseline.

### 7.2 SAFETY AND TOLERABILITY VARIABLES

Safety and tolerability will include Adverse Events, physical examination, body weight, vital signs and compliance.

- Adverse events will be recorded throughout the study.
- Physical examination including neck exam, cardiac exam and respiratory exam will be performed at screening and final visits. Body weight will also be recorded at screening, baseline, and final visit.

- Vital signs including heart rate, systolic and diastolic blood pressure will be performed at screening and final visits.
- Patients' compliance with Tirosint® and with the prescribed treatments (levothyroxine as per prescription during the run-in and PPI during the run-in and throughout the whole treatment period) will be assessed by visit based on data reported in the Subject's Diary; Tirosint® compliance will also be assessed by visit based on the Drug Administration.

### 7.3 CONCOMITANT MEDICATIONS

Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 and Preferred Term (PT) assigned from the WHO drug terms and procedures dictionary for treatments and surgical and medical procedures, showing the number and percentage of subjects from the Safety Population taking each medication. Prior and concomitant LT4/PPI treatments will be summarized separately.

### 7.4 LABORATORY DATA

Laboratory data will include:

- blood sampling for thyroid function tests: TSH, FT4, TT4, FT3, TT3;
- serum laboratory tests: CPK, SHBG, ferritin, ACE, and lipid panel (TC, HDL-C, LDL-C, VLDL-C, TG);

## 8 HANDLING OF MISSING AND INCOMPLETE DATA

Cases of withdrawal from the study, for any reasons, after inclusion will not be replaced. However, the withdrawn cases will be analyzed in the ITT analysis.

TSH, FT4, TT4, FT3, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel (TC, HDL-C, LDL-C, VLDL-C, TG) values recorded after changes in LT4 dose will not be considered for the statistical analysis.

For analyses that require complete patient data, missing values during the treatment period will be replaced, for all primary and secondary variables, with the Last Observation Carried Forward (LOCF) technique. Imputed values will be included in the analysis set(s), but will not change the original clinical database.

#### Partial dates imputation:

##### *Prior and Concomitant Medications*

Partial start dates will be computed as follow:

- If day is missing the first day of the reported month will be imputed.
- If month and day are missing the 1<sup>st</sup> January will be imputed.
- If month, day and year are missing no imputation will be applied.



Partial end dates will be computed as follow:

- If day is missing the last day of the reported month will be imputed.
- If month and day are missing the 31<sup>st</sup> December will be imputed.
- If month, day and year are missing no imputation will be applied.

Prior and concomitant medications without an end date will be considered as ongoing.

*Adverse Events*

Partial start dates will be computed as follow:

- If day is missing the first day of the reported month will be imputed.
- If month and day are missing the 1<sup>st</sup> January will be imputed.
- If month, day and year are missing no imputation will be applied.

Partial end dates will be computed as follow:

- If day is missing the last day of the reported month will be imputed.
- If month and day are missing the 31<sup>st</sup> December will be imputed.
- If month, day and year are missing no imputation will be applied.

Adverse events without an end date will be considered as ongoing.



## **9 STATISTICAL METHODOLOGY**

### **9.1 GENERAL METHODOLOGY**

#### Descriptive statistics

- Continuous variables will be summarized by mean, standard deviation, median, 1<sup>st</sup> quartile, 3<sup>rd</sup> quartile, minimum and maximum.
- Discrete variables will be summarized by frequencies and percentages.

All p-values will be rounded to four decimal places. Statistical significance will be declared if the two tailed p-value is less than 0.050.

#### Baseline definition

As baseline will be considered the last assessment before the first dose of study treatment. (i.e. date of assessment previous or equal to the start date of study treatment)

### **9.2 PATIENT DISPOSITION**

A complete screening disposition on screened patients including the number of enrolled patients, the number of screening failure, the number of patients rescreened and the reason for screening failure will be provided.

A study disposition will also be provided, it will include number of patients who completed or discontinued the study and the reason for discontinuation.

Disposition of patients who performed each visit, patients included in each analysis population and protocol deviations will be provided. To evaluate the COVID-19 impact on the study a summary of protocol deviations related to it will be provided.

### **9.3 DEMOGRAPHIC AND SCREENING/BASELINE CHARACTERISTICS**

Demographic data will include age, height, weight, BMI: those will be analyzed as summary of means. Gender and race will also be analyzed as summary of frequencies and percentages.

Patients baseline characteristics will include:



- Prior medications: those will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 and Preferred Term (PT). Prior LT4/PPI treatments will be summarized separately.
- Medical and surgical history information: those will be summarized by System Organ Class (SOC) and Preferred Term (PT).
- Childbearing potential and urine pregnancy test information that will be summarized by frequencies and percentages on female patients of the following variables: childbearing potential and information about lactating, using reliable contraception, pregnancy in the next months and pregnancy test.

#### 9.4 ANALYSIS OF EFFICACY

All efficacy variables will be analyzed in the ITT, mITT and PP populations.

##### 9.4.1 Primary efficacy analysis

The primary efficacy endpoint is the change in serum levels of TSH at the end of the 12-week treatment period with Tirosint® capsules vs baseline.

A mixed model ANCOVA repeated measures model will be used to test differences in means of TSH level at Visit 4 vs baseline visit. As covariates will be considered the following baseline variables: Age, Sex, BMI and the prescribed Tirosint® dosage (dose/Kg). Unstructured covariance structure will be used (If a different type of covariance structure will be used details will be provided).

Normal distribution for the TSH data will be tested with Shapiro Wilks.

If TSH data results not to be distributed as a normal distribution the following methods will be applied:

- Data will be log transformed and analyzed with the ANCOVA repeated measures model described above.

The TSH level at each time point will also be summarized as continuous variable.

The primary efficacy analysis will be performed on data with missing values replaced with LOCF method and on original data (values recorded after changes in LT4 dose will not be considered in either case).

##### 9.4.2 Secondary efficacy analysis

- Serum levels of FT4, FT3, TT4, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel (TC, HDL-C, LDL-C, VLDL-C, TG) at the end of each 12-week treatment period vs baseline

The secondary efficacy endpoints are the changes in serum levels of FT4, FT3, TT4, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel (TC, HDL-C, LDL-C, VLDL-C, TG) at the end of each 12-week treatment period with Tirosint® capsules vs baseline.

Mixed model ANCOVA repeated measures models will be used to test differences in means of serum levels of FT4, FT3, TT4, TT3, CPK, SHBG, ferritin, ACE level, at Visit 4 vs baseline visit. As covariates will be considered the following baseline variables: Age, Sex, BMI and the prescribed Tirosint® dosage (dose/Kg). Unstructured covariance structure will be used (If a different type of covariance structure will be used details will be provided).

Normal distributions for each serum level data will be tested with Shapiro Wilks. If data results not to be distributed as a normal distribution the following methods will be applied:

- Data will be log transformed and analyzed with the ANCOVA repeated measures models described above.

- The change in serum levels of TSH, FT4, FT3, TT3 at Visit 3 vs baseline

Mixed model ANCOVA repeated measures models will be used to test differences in means of serum levels of TSH, FT4, FT3, and TT3 at Visit 3 vs baseline visit. As covariates will be considered the following baseline variables: Age, Sex, BMI and the prescribed Tirosint® dosage (dose/Kg). Unstructured covariance structure will be used (If a different type of covariance structure will be used details will be provided).

Normal distributions for each serum level data will be tested with Shapiro Wilks. If data results not to be distributed as a normal distribution the following methods will be applied:

- Data will be log transformed and analyzed with the ANCOVA repeated measures models described above.

The serum levels of TSH, FT4, FT3, TT4, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel at each time point will also be summarized as continuous variables.

- LT4 dose adjustment

Frequencies and percentages of patients requiring changes in LT4 daily dose during the treatment period will be provided.

Changes in mean LT4 daily dose/kg at the end of the treatment period versus baseline will be analyzed by a mixed model ANCOVA repeated measures model with LT4 daily dose/kg at each time point as dependent variable. Unstructured covariance structure will be used (If a different type of covariance structure will be used details will be provided).

Normal distribution for the LT4 daily dose/kg data will be tested with Shapiro Wilks.

If LT4 daily dose/kg data results not to be distributed as a normal distribution the following methods will be applied:

- Data will be log transformed and analyzed with the ANCOVA repeated measures model described above.

The secondary efficacy analysis will be performed on data with missing values replaced with LOCF method and on original data (values recorded after changes in LT4 dose will not be considered in either case).

## 9.5 ANALYSIS OF SAFETY

The safety analyses will be carried out in the safety population.

### 9.5.1 Tolerability parameters

Laboratory parameters will be summarized for each visit by means of descriptive statistics. Changes from baseline and 95% confidence interval on mean change will also be provided. Frequencies and percentages of low, normal and high values for each parameter at each time point will also be provided. Laboratory data will also be listed with clinically significant information.

Physical examinations will be summarized as frequency and percentages of normal and abnormal body system at each time point. Weight and BMI will be summarized by means of descriptive statistics and changes from baseline.

### 9.5.2 Adverse Events

Adverse events (AEs) intensity and frequency will be analysed during the pre-treatment phase and in the treatment phase until End of Study Visit.

The following summary tables will be provided:

- Adverse Events by SOC and PT;
- Serious Adverse Events by SOC and PT;

- Drug related Adverse Events by SOC and PT;
- Pre-Treatment Adverse Events by SOC and PT;
- Serious Pre-Treatment Adverse Events by SOC and PT;
- Treatment-Emergent Adverse Events by SOC and PT;
- Serious Treatment-Emergent Adverse Events by SOC and PT;
- Drug related Treatment-Emergent Adverse Events by SOC and PT;

Serious adverse events and fatal adverse events will also be listed.

### 9.5.3 Vital signs

Vital signs (including heart rate, systolic and diastolic blood pressure) and body weight will be analyzed by means of descriptive statistics. Moreover mean change from baseline and 95% confidence interval on mean change will also be provided.

### 9.5.4 Other tolerability parameters

#### Treatment compliance

- Patients' compliance with Tirosint® and with the prescribed treatments (levothyroxine as per prescription during the run-in and PPI during the run-in and throughout the whole treatment period) will be assessed based on data reported in the Subject's Diary, calculating the percentage of medication taken in relation to the actual period of treatment (number of doses reported to be taken during the period / number of doses envisaged to be taken during the period x 100).
  - Number of doses reported to be taken during the period will be computed as number of days through the visits reported with dose taken = "Yes" in the Subject's Diary.
  - Number of doses envisaged to be taken during the period will be computed as number of days from the previous visit to the next one.

Patient who didn't fill in Subject's Diary for at least one visit will not be considered for this analysis and compliance will be considered not evaluable.

- Patients' compliance with Tirosint® will also be assessed on the Drug Administration, calculating the percentage of medication taken in relation to the recommended dose and the actual period of treatment (total amount of drug actually taken during the period / total amount of drug envisaged to be taken during the period x 100).

- Amount of drug actually taken will be computed from the drug accountability as sum of used amount of drug returned and used amount of drug not returned x related drug dosages.
- Amount of drug envisaged to be taken will be computed as prescribed dosage x period time.

Compliance will be defined as:

- *excellent* for consumption of study drug  $\geq 95\%$  of the amount envisaged.
- *good* for consumption  $\geq 90$  and  $< 95\%$ ;
- *poor* for values lower than 90%.

Compliance will be evaluated separately by visit.

Treatment compliance will be analyzed by means of descriptive statistics for:

- Tirosint® compliance from Subject Diary
- Tirosint® compliance by visit from Subject Diary
- LT4 compliance from Subject Diary
- LT4 compliance by visit from Subject Diary
- Tirosint® compliance from Drug accountability
- Tirosint® compliance by visit from Drug accountability
- PPI compliance from Subject Diary
- PPI compliance by visit from Subject Diary

Frequencies and percentages of patients' compliance classification (excellent, good or poor) will be provided for Tirosint® compliance from drug accountability data.

#### Drug dosage

Tirosint® mean Daily dosage and mean Daily dosage/Body Weight will be analyzed by means of descriptive statistics at each time point.

## 9.6 INTERIM ANALYSIS



No interim analyses were planned.





## **10 GENERAL CONSIDERATIONS**

### **10.1 SOFTWARE TO BE USED**

All statistical analyses will be performed using SAS® Software (release 9.4) on a [REDACTED] Operating system. Data-Entry and Data Management were performed using [REDACTED].

### **10.2 CODING DICTIONARIES**

Adverse events and previous/concomitant pathologies will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™ 21.1 Version), while prior and concomitant medications will be coded using WHO-Drug Dictionary (Version of 2018 September).

### **10.3 PROGRAMS QUALITY CONTROL**

The Study Statistician – programmer of the tables and listings will perform checks to ensure that the output of the statistical analysis process, including both analysis programs (e.g. the log files should be free from error messages or unexpected warnings) and results, is accurate and bias are minimised.

A second Statistician, not involved in the trial analysis, will thoroughly check and test all analysis programs, in particular for code obtained from external sources.

He will ensure that the outputs created by each program are clear and contain correct data, that the programs are executed on the latest version of the clinical database and that the analyses are carried out in accordance with the SAP.

## 11 REFERENCES

13US-T404 Study Protocol (Version 6.0, 17 June 2019).

13US-T404 Case Report Form (Version 3.0 – 05 November 2018).

13US-T404 Patient's Diary (Version 2.0 – 20 July 2018).

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## 12 PROGRAMMING SPECIFICATIONS

Not applicable.

## 13 APPENDIX 1: LIST OF TABLES, LISTINGS AND FIGURES

Not applicable.

**14 APPENDIX 2: SHELL TABLES**

Not applicable.

