

### CLINICAL TRIAL PROTOCOL

INVESTIGATIONAL MEDICINAL PRODUCT (IMP):	Tirosint® (levothyroxine sodium) capsules
PROTOCOL N°:	13US/T404
EUDRACT N°:	Not Applicable
REGISTRY NAME AND ID (IF APPLICABLE):	ClinicalTrials.gov Identifier: NCT03094416
TITLE:	An open-label therapeutic efficacy study of Tirosint® (levothyroxine sodium) capsules in thyroidectomized patients taking proton pump inhibitors.
SPONSOR:	IBSA, Institut Biochimique S.A. Via del Piano 6915 Pambio-Noranco (Switzerland) [REDACTED]
SPONSOR STUDY MANAGER:	[REDACTED]
CO-ORDINATING INVESTIGATOR:	[REDACTED]
DOCUMENT VERSION:	Final 6.0
DOCUMENT DATE:	17JUN2019
This study will be performed in compliance with Good Clinical Practices, including the archiving of essential documents	
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## DOCUMENT HISTORY

Version Number	Date of issue	Short description of change/s and cross reference to eventual protocol amendment number
2.0	08APR2016	First version signed by the Investigator (previous versions were only circulated among the Sponsor, the Investigator and the CRO). Never submitted to IRB.
3.0	14SEP2016	First version submitted to IRB
4.0	04JAN2017	<p>Amendment N.1</p> <p>§1: expected study start date has been updated.</p> <p>§5.2: inclusion criterion I6 has been modified in order to reduce the duration of PPI therapy from 3 months to 8 weeks before screening visit.</p> <p>§6.5: clarification on the consumption of restricted foods has been added.</p> <p>§7.2: clarification about the requirements for dating consent form has been added.</p> <p>§10, §10.1: requirements for reporting of SAEs to FDA have been updated according to applicable regulations. Some clarifications on AEs/SAEs reporting have been added.</p> <p>§10.2: clarifications to reporting requirements for pregnancy have been added.</p> <p>Appendix I: corrections in the wording have been done.</p>
5.0	15JUN2018	<p>Amendment N. 2</p> <p>Expected date of last patient last visit has been extended from March 2018 to to July 2019</p> <p>Several sections of the protocol have been modified in order to take into account the suggestions raised during the</p>



	<p>Investigators' Meeting held on February 26<sup>th</sup> 2018:</p> <ul style="list-style-type: none"><li>- LT4 dose adjustments have been allowed, if TSH levels &gt; 10 or &lt; 0.01 mIU/L at control visits (interim or unforeseen) after inclusion.</li><li>- Reasons for withdrawal have been updated accordingly.</li><li>- LT4 dose adjustment has been added as a parameter of evaluation, secondary efficacy variable and study objective.</li><li>- Statistical analysis has been update accordingly.</li><li>- Other proton pump inhibitors (dexlansoprazole ≥ 30 mg daily and rabeprazole ≥ 20 mg daily) have been allowed.</li><li>- Use of over-the-counter PPIs has been allowed, if so directed by the prescribing doctor.</li><li>- Glucocorticoids have been allowed if at stable doses throughout the entire study duration (from screening to final visit).</li><li>- The request to interrupt intake of biotin for 2 days before the baseline (V2) and the final (V4) visits has been added.</li><li>- Information on timelines for samples shipment within 7 days from collection have been added.</li></ul> <p>Several sections of the protocol have been modified to take into account the revision of the Prescribing Information of Tirosint (dated 04/2017) and all levothyroxine products:</p> <ul style="list-style-type: none"><li>- Introduction on drug interactions reported for levothyroxine has been updated.</li><li>- Mode of administration of Tirosint has been updated.</li><li>- Information on the interval for serum TSH levels monitoring has been shortened from 12 to 6-8 weeks.</li><li>- Information on Pregnancy and Lactation has been updated.</li><li>- The 175 and 200 mcg strengths of Tirosint have</li></ul>
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		<p>been added.</p> <ul style="list-style-type: none"> <li>- Forbidden medications as well as precautions to be adopted with use of concomitant medications and foods have been updated.</li> </ul> <p>Some inaccuracies and misspellings have been corrected throughout the text.</p>
6.0	17JUN2019	<p>Amendment N. 3</p> <p>Expected date of last patient last visit has been extended from July 2019 to April 2020.</p> <p>Age at inclusion has been extended from 65 to 75 years (Inclusion Criterion I2).</p> <p>The possibility to re-screen the subjects because of wash-out from forbidden medications has been deleted, as per Protocol Memo dated 04-Oct-2018.</p> <p>Following to a revision of the Prescribing Information of Tirosint capsules (dated 06/2018):</p> <ul style="list-style-type: none"> <li>- Reference to the Prescribing Information of Tirosint capsules has been modified from version [REDACTED] to version "IBSA Pharma Inc 2018".</li> <li>- The distributor of Tirosint capsules has been changed from [REDACTED] to IBSA Pharma Inc, Parsippany, NJ 07054, USA.</li> <li>- The number of capsules to be dispensed at each visit has been changed from 56 to 60; the number of capsules per blister has been changed from 7 to 10; the number of capsules per box has been changed from 28 to 30.</li> </ul> <p>The signature of ICF in two originals (one for the Investigator and one for the subject) has been substituted by the signature of ICF in single copy, with original archived by the Investigator and copy given to the subject.</p> <p>The list of documents to be retained in the ISF and TMF has been updated.</p>



## PROTOCOL SUMMARY

<b>Title:</b>	An open-label therapeutic efficacy study of Tirosint® (levothyroxine sodium) capsules in thyroidectomized patients taking proton pump inhibitors.
<b>Protocol N°:</b>	13US/T404
<b>Study Site(s):</b>	Coordinating site: [REDACTED] [REDACTED] Additional sites information are provided separately.
<b>Study Objectives:</b>	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.
<b>Study Population:</b>	A maximum number of 60 (at least 48 completed) adult patients with a history of hypothyroidism due to total thyroidectomy, who are 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 or associated gastrointestinal issues on prescription proton pump inhibitors (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.
<b>Study Design:</b>	This is an open-label, phase IV study.
<b>Treatment:</b>	Tirosint® (levothyroxine sodium) 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 mcg capsules [REDACTED]). The drug will be given at the same pre-study dose. Proton pump inhibitors as prescribed.
<b>Evaluation parameters:</b>	During the <i>screening visit</i> , subjects (holding their morning dose of LT4) will undergo screening serum measurements for TSH, FT4, FT3 and TT3, along with a physical examination. Subjects complying with inclusion/exclusion criteria will enter a run-in period, in which they will continue taking their levothyroxine and proton pump inhibitor medications as per prescription, at their current dose. Should the patient require LT4 dose adjustment at screening visit, it will be possible to re-screen the patient until thyroid function tests normalization under the new dose. Four to 6 weeks later, subjects (fasting and holding

their morning dose of LT4) will undergo *baseline* serum measurements of TSH, FT4, TT4, FT3, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel (TG, TC, HDL, LDL, and VLDL) as baseline thyroid function related serum laboratory assessments. Patients will then be switched to Tirosint® capsules at the same daily dose. Patients will remain on Tirosint® for 12 weeks (time frame allowed: 11-13 weeks) and will continue their regular intake of proton pump inhibitor, throughout the whole study duration, according to prescription. Tirosint® will be taken as a single daily dose in the morning, on an empty stomach, one-half to one hour before breakfast. All subjects will separate their LT4 by at least 4 hours from any drug known to interfere with LT4 absorption (i.e. iron and calcium supplements, bile acid sequestrants and ion exchange resins) and by at least 1 hour from foods that are known to interfere with LT4 absorption.

Halfway through the Tirosint® treatment period (time frame allowed: 5-7 weeks), subjects will report to the clinical center and (holding their morning dose of LT4) will undergo *intermediate* serum measurements of TSH, FT4, FT3 and TT3, for safety assessment.

At the end of the 12 week Tirosint® treatment period, patients will report to the study site for the *final visit* and (fasting and holding their morning dose of LT4) they will undergo 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 will be evaluated throughout the study by adverse event monitoring.

**Primary end-point:**

Change in serum levels of TSH at the end of the 12-week Tirosint® treatment period with respect to its baseline.





**Secondary end-points:**

*Efficacy assessments:*

Change in serum levels of FT4, TT4, FT3, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel at the end of the 12-week Tirosint® treatment period with respect to its baseline.

Serum levels of TSH, FT4, FT3 and TT3 halfway through each treatment cycle.

LT4 dose adjustment 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 the baseline.

*Safety assessments:*

Adverse events

Vital signs

Body weight

**Statistical analysis:**

*Primary Efficacy Analysis*

The primary efficacy end-point will be the change in serum levels of TSH at the end of the 12-week treatment period with Tirosint® capsules with respect to baseline.

The serum levels of TSH will be analyzed by means of a repeated measures analysis of covariance on the difference (final vs baseline visit) with basal value as covariate. The 95% confidence interval will be calculated. Additional non-parametric analyses may be performed on the evolution of TSH serum levels as sensitivity analyses.

Baseline variables (e.g. gender, pre-study LT4 product, LT4 dose, proton pump inhibitor product and dose, etc.) may also be used as covariates if appropriate.

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

*Secondary Efficacy Analyses*

The secondary efficacy end-points will be the change in



serum levels of FT4, TT4, FT3, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel at the end of each 12-week treatment period with Tirosint® capsules with respect to baseline. The change in serum levels of TSH, FT4, FT3, TT3 at Visit 3 with respect to baseline will also be analyzed as secondary efficacy end-points.

Serum levels of FT4, TT4, FT3, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel (TC, HDL-C, LDL-C, VLDL-C, TG) will be analyzed by means of a repeated measures analysis of covariance with basal value as covariate.

The 95% confidence interval will be calculated.

Baseline variables (e.g. gender, pre-study LT4 product, LT4 dose, proton pump inhibitor product and dose, etc.) may also be used as covariates if appropriate.

The secondary end-point parameters recorded after changes in LT4 dose will not be considered for the analysis.

The dose adjustment evaluated in terms of number of patients requiring changes in LT4 daily dose during the treatment period will be described using frequencies and percentages.




Changes in mean LT4 daily dose at the end of the treatment period versus baseline will be analyzed by means of a repeated measure analysis of variance model.

#### *Safety Analyses*

Numbers of patients experiencing Adverse Events (AEs) will be calculated. AEs will be classified using MedDRA categories. Vital signs 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 calculated.

<b>Expected starting date:</b>	Expected date of first patient first visit: January 2017
<b>Expected ending date:</b>	Expected date of last patient last visit: April 2020

## OVERALL STUDY SCHEDULE

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 will be 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.

## LIST OF ABBREVIATIONS

ACE.....	Angiotensin Converting Enzyme
AE .....	Adverse Event
ANCOVA.....	Analysis of covariance
ANOVA .....	Analysis of Variance
BP.....	Blood Pressure
BW .....	Body Weight
CI.....	Confidence Interval
Cmax .....	Maximum plasma concentration
CPK.....	Creatine Phosphokinase
CRF .....	Case Report Form
CRO .....	Clinical Research Organisation
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
LT4.....	Levothyroxine
MAH .....	Marketing Authorization Holder
MW .....	Molecular Weight
NIMP.....	Non-Investigational Medicinal Product
OTC.....	Over-The-Counter
PPI.....	Proton Pump Inhibitor
R&D.....	Research and Development
Rx.....	Prescription drug
SAE .....	Serious Adverse Event
SAP .....	Statistical Analysis Plan
SHBG.....	Sex-Hormone Binding Globulin
T3 .....	Triiodothyronine
T4 .....	Thyroxine
TBG.....	Thyroxine-Binding Globulin
TC.....	Total Cholesterol
TFT.....	Thyroid Function Test
TG .....	Triglycerides
Tmax .....	Time to achieve Cmax
TSH.....	Thyroid Stimulating Hormone
TT3.....	Total Triiodothyronine





TT4..... Total Thyroxine  
VLDL-C..... Very Low-density Lipoprotein Cholesterol  
WHO-DD..... WHO Drug Dictionary  
WIC..... Written Informed Consent





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## APPENDICES

APPENDIX I	Adverse Events Form/Guidance for classification <i>Serious Adverse Event Form/Guidance for completion</i>
APPENDIX II	Representative written information for patient and sample written informed consent form
APPENDIX III	Responsibilities of the Clinical Investigators







## 1 ORGANISATIONAL AND ADMINISTRATIVE ASPECTS

### STUDY SITE

Subject screening, enrolment and follow-up, as well as blood and urine samples collection will be performed at:

[REDACTED]

Principal Investigator: [REDACTED]  
[REDACTED]

[REDACTED] will also act as Coordinating Study Site.

Additional sites and Investigators participating in the study are listed in a separate document and require approval by Institutional Review Board/Ethics Committee.

### LABORATORY

Clinical analyses will be performed by (receiving lab):

[REDACTED]

Specialized labs of [REDACTED] may perform specific analyses.

### STUDY MONITORING

[REDACTED]



DATA MANAGEMENT

IBSA Institut Biochimique SA

[Redacted text block]

STATISTICAL ANALYSIS

[Redacted text block]

DRUG SAFETY

IBSA Institut Biochimique SA

[Redacted text block]

CLINICAL QUALITY ASSURANCE

IBSA Institut Biochimique SA

[Redacted text block]

SPONSOR REPRESENTATIVE

IBSA Institut Biochimique S.A.

[Redacted text block]





[REDACTED]

SPONSOR MEDICAL EXPERT

[REDACTED]

EU LEGAL REPRESENTATIVE (or US REPRESENTATIVE)

Not applicable

No Data Monitoring Committee or Steering Committee are foreseen.

Expected study start: January 2017 (expected date of first patient)

Expected study end: April 2020 (expected date of last patient last visit)



## 2 INTRODUCTION

### 2.1 Background Information

Primary hypothyroidism or thyroid hormone deficiency due to abnormality in the thyroid gland is the most common endocrine disease. The prevalence of hypothyroidism in the general population ranges from 3.8% to 4.6% ([Chakera, Pearce et al. 2012](#)).

In Western countries, the most common cause of primary hypothyroidism is autoimmune thyroiditis. However, in many parts of the world, iodine deficiency remains an important cause. Other common causes of hypothyroidism include thyroidectomy, radioiodine therapy, and drugs such as amiodarone, lithium, thionamide, iodine, interferon, sunitinib, rifampicin, and thalidomide.

Diagnosis and treatment of hypothyroidism is often considered simple and is mostly carried out in a primary care setting. However, studies continue to show problems in the management of this condition. Many patients on thyroid hormone replacement are either under-replaced or over-replaced and a significant number of patients on thyroid hormone replacement report not feeling well despite having thyroid function tests (TFTs) within the healthy reference range.

The common clinical features associated with hypothyroidism are tiredness, weight gain, dry skin, cold intolerance, constipation, muscle weakness, puffiness around the eyes, hoarse voice, and poor memory.

Overt primary hypothyroidism is diagnosed biochemically with a serum thyroid stimulating hormone (TSH) concentration above the reference range and low free thyroxine (FT4). The population reference range of TSH is around 0.4–4.5 mIU/L and most patients with overt hypothyroidism have TSH above 10 mIU/L. However, several controversies surrounding the TSH reference range have surfaced in recent years. Firstly, because the TSH in the general population is not normally distributed, and more than 95% of healthy individuals have TSH less than 2.5 mIU/L, it has been suggested that the upper limit of the TSH reference range should be lowered from 4.5 to 2.5 mIU/L ([Wartofsky and Dickey 2005](#)).

Levothyroxine (LT4) is the treatment of choice for hypothyroidism. It has a 7-day half-life, allowing daily dosing. In patients with no significant comorbidities, initiation of LT4 at a full dose based on body weight (1.6 mcg/kg/day) is usually safe and effective.

Food can interfere with the absorption and action of levothyroxine. Conventionally, hypothyroid patients are advised to take LT4 on an empty stomach at least half an hour before breakfast to prevent impairment of absorption by food.

Moreover, several medications are known to affect the level of serum thyroid hormone in patients with hypothyroidism receiving LT4 replacement, either by reducing gastrointestinal absorption of LT4 or by increasing its metabolic clearance.

Common drugs that can affect LT4 absorption include iron, calcium, bile acid sequestrants and ion exchange resins and LT4 must be taken at least 4 hours apart from these drugs. Orlistat, aluminum and magnesium hydroxides and simethicone are also known to decrease levothyroxine absorption.

Enzyme inducers, such as phenobarbital, and rifampin can increase the metabolism of levothyroxine, resulting in an increased dose requirement, while enzyme inhibitors such as beta-adrenergic agonists, glucocorticoids and amiodarone decrease the peripheral conversion of T4 to T3, leading to decreased T3 levels. Other drugs may alter the serum transport of thyroid hormones therefore requiring monitoring of thyroid hormone parameters.

Gastric acidity is an essential requirement for adequate absorption of levothyroxine. Sucralfate, antacids and proton pump inhibitors (PPIs) may cause hypochlorhydria, affect intragastric pH, and reduce levothyroxine absorption, therefore requiring appropriate monitoring of patients (IBSA Pharma Inc 2018).

PPIs are commonly used to treat conditions such as gastric and duodenal ulcers, *Helicobacter pylori* infection, and gastroesophageal reflux disease (AstraZeneca 2016).

Centanni et al. reported that omeprazole treatment was associated with an increase in the level of serum TSH in 10 patients treated with LT4, an effect that was reversed by an increase in the LT4 dose by 37% (Centanni, Gargano et al. 2006).

Similarly, Sachmechi et al demonstrated that lansoprazole affected TSH levels in patients with primary hypothyroidism receiving LT4 replacement therapy (Sachmechi, Reich et al. 2007). In the study group, 19% of the patients required an adjustment of LT4 dose after lansoprazole therapy was initiated, and the mean increase in LT4 dose was 35%.

Recently, an epidemiology study performed in the United Kingdom demonstrated significant interaction between levothyroxine and PPIs with serum TSH increasing of 0.12 mU/L and a clinically significant increase of over 5 mU/L in serum TSH presented by 5.6% of the patients (Irving, 2014). A second epidemiology study performed in Italy, also showed a significant increase of TSH levels during initial exposure to potentially interacting drugs, including PPIs, and an increased use of levothyroxine (Trifirò, Parrino et al. 2015).

The proposed mechanism for increased TSH levels during PPI therapy is a reduction in gastrointestinal absorption of LT4 due to reduction of gastric acid secretion (Centanni, Gargano et al. 2006).

## 2.2 Rationale

Tirosint (levothyroxine sodium) capsule has been proven to be bioequivalent to Synthroid tablets in healthy volunteers administered 600 mcg of LT4 in single dose (Colucci, D'Angelo et al. 2011).

A study by Pabla et al demonstrated that the *in vitro* dissolution profile of Tirosint capsule is less influenced by the pH of the medium with respect to Synthroid and a generic tablet (Pabla, Akhlaghi et al. 2009).

Following to this *in vitro* report, it has been recently demonstrated in healthy volunteers administered 600 mcg of LT4 in single dose, that absorption of LT4 is less influenced by i.v. infusion of 80 mg esomeprazole when administered in the form of Tirosint capsule than of Synthroid tablet (Seng Yue et al, 2015).

This pilot study is aimed at assessing whether the *in vitro* and *in vivo* reports are confirmed in the clinical setting of hypothyroid patients.

### **2.3 Potential risks and benefits**

In this study the patients will continue their therapy with LT4 and with PPIs at the prescribed doses, therefore no safety concern is advised.

The risk of switching from one LT4 formulation to another is minimized by the check of TFTs after 6 and 12 weeks from the switch, as recommended in clinical practice.

Should the hypothesis be demonstrated, the patients may benefit from a better controlled serum TSH. The study may benefit the overall population in the future.

## **3 TRIAL OBJECTIVES**

### **3.1 Primary objective (s)**

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.

### **3.2 Secondary objective(s)**

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 TRIAL DESIGN**

This will be an open-label, phase IV study.

Enrolment will be stopped as soon as 48 patients are completed or 60 patients are included in the Tirosint treatment phase, whatever comes first.

Adult patients with a history of hypothyroidism due to total thyroidectomy, who are 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 will be included in the study.

During the screening visit, subjects (holding their morning dose of LT4) will undergo screening serum measurements for TFTs (TSH, FT4, free T3 [FT3], total T3 [TT3]), along with a physical examination. Subjects complying with inclusion/exclusion criteria will enter a run-in period, in which they will continue taking their levothyroxine and PPI medications as per prescription, at their current dose. Should the patient require LT4 dose adjustment at screening visit, it will be 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) will undergo 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 will then be switched to Tirosint® capsules at the same daily dose.

Patients will remain on Tirosint® for 12 weeks (time frame allowed: 11-13 weeks) and will continue their regular intake of Rx PPI, throughout the whole study duration, according to prescription.

Tirosint® will be taken as a single daily dose in the morning, on an empty stomach, one-half to one hour before breakfast. All subjects will separate their LT4 by at least 4 hours from any drug known to interfere with LT4 absorption (e.g. iron and calcium supplements), and by at least 1 hour from foods that are known to interfere with LT4 absorption.

Halfway through the Tirosint® treatment period (time frame allowed: 5-7 weeks), subjects will report to the clinical center and (holding their morning dose of LT4) will undergo intermediate serum measurements of TSH, FT4, FT3, TT3, for safety assessment.

At the end of the 12 week Tirosint® treatment period, patients will report to the study site for the final visit and (fasting and holding their morning dose of LT4) they will undergo 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 will be evaluated throughout the study by adverse event monitoring.

#### *Study design and study population*

The study has been designed as a preliminary evaluation in patients, therefore an open-label, non-randomized design has been judged appropriate.

Each patient's control will be the baseline evaluation with their standard therapy.

Thyroidectomized patients have been selected being the endogenous production of thyroid hormones absent; therefore, circulating thyroxine (T4) is of exogenous origin only.

Patients with GERD or associated gastrointestinal issues have been selected as these are common pathologies, which are usually treated with PPIs.

#### *Choice of the doses*

The doses between 88 and 250 mcg have been selected because patients who have had a thyroidectomy are usually treated with dosages above 88 mcg, while patients in treatment with unusually high doses of LT4 (greater than 250 mcg) may have other underlying factors affecting absorption of the drug.

The strengths of omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole and rabeprazole have been selected based on the Prescribing Information of the authorized products. Only prescription (Rx) products (either brand or generics) will be accepted, since over-the-counter (OTC) products are authorized only for short-term treatment (not more than 14 days every 4 months), unless directed by the prescribing doctor.

#### *Choice of evaluation parameters and timing for evaluations*

Pharmacological therapy with synthetic levothyroxine is currently monitored and adjusted on the basis of the FT4 and TSH serum levels. TSH is a widely recognized marker of thyroid function status. Therefore it has been selected as primary efficacy outcome and as indicator of LT4 absorption. Additional laboratory tests related to thyroid hormone status will be evaluated.

The peak therapeutic effect of a given dose of levothyroxine may not be attained for 4 to 6 weeks. In adult patients with primary hypothyroidism, it is recommended to monitor serum TSH levels after an interval of 6 to 8 weeks after any change in dose ([IBSA Pharma Inc 2018](#)). Therefore in the study the first (intermediate) visit will be performed 6 weeks after switch to Tirosint, for safety purposes and the final visit will be performed 12 weeks after switch, when TSH is supposed to be stabilized.



### *Patients safety*

The patients will be administered the same pre-screening dose of LT4 according to the approved modalities; therefore no adverse events (AEs) due to LT4 are expected. Moreover, safety checks of TFTs will be performed every 6 weeks upon switch to Tirosint and, should TSH levels > 10 or < 0.01 mIU/L be measured, a dose adjustment will be allowed.

Proton pump inhibitors therapy will also be continued at the same pre-screening dose and as per the prescribed modalities. Therefore, a safety concern is not advised.

### *Pregnancy and breastfeeding*

Experience with levothyroxine use in pregnant women, including data from post-marketing studies, have not reported increased rates of major birth defects or miscarriages, while there are risks to the mother and fetus associated with untreated hypothyroidism in pregnancy. Therefore levothyroxine should not be discontinued during pregnancy. Nevertheless, since TSH levels may increase during pregnancy, TSH should be monitored and levothyroxine dosage adjusted during pregnancy.

There is insufficient information to determine the effects of levothyroxine on the breastfed infant and no available information on the effects of levothyroxine on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for levothyroxine and any potential adverse effects on the breastfed infant from levothyroxine or from the underlying maternal condition (IBSA Pharma Inc 2018).

Regarding PPIs, their safety of use in pregnancy and lactation varies depending on the active ingredient. Nevertheless, there are no adequate and well-controlled studies with each PPI in pregnant women. In addition, at least for some PPIs, harm to the nursing infant cannot be excluded (e.g. [Takeda Pharmaceuticals America Inc. 2017](#)).

Taking in consideration the above information, only non-pregnant and non-lactating females will be included in the study. Should a pregnancy onset after inclusion, the patient will drop out of the study.

## **5 SELECTION OF POPULATION**

### **5.1 Subjects selection**

A maximum number of 60 adult patients will be enrolled in this study, in order to have at least 48 patients completed.

The Clinical Investigator is to give his/her approval to the participation of each subject in the study on the basis of acceptable medical history and findings in the physical examination and laboratory investigations which comply with the inclusion/exclusion criteria below.

## 5.2 Inclusion criteria

Inclusion in the study requires compliance with all the following criteria for inclusion:

- I1. written informed consent duly read, signed and dated by the subject;
- I2. aged  $\geq 18$  and  $\leq 75$  years;
- I3. history of hypothyroidism due to total thyroidectomy;
- I4. on stable LT4 tablet doses for at least 6 weeks at screening ( $\geq 88$  mcg daily and  $\leq 250$  mcg daily);
- I5. TSH at screening  $\geq 0.3$  and  $\leq 4.0$  mIU/L<sup>1</sup>;
- I6. history of gastroesophageal reflux disease or associated gastrointestinal issues on prescription<sup>2</sup> 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 and for whom chronic therapy with PPIs for the next 5 months has been prescribed;
- I7. for women, adequate and continuative contraceptive measures<sup>3</sup> until the end of the study, if not in menopause;
- I8. reasonable assumption of understanding the study and willingness to take part to the study and to comply with protocol requirements.

## 5.3 Exclusion criteria

The presence of any of the following criteria for exclusion will mean that the patient is not eligible for inclusion in the study:

- E1. suspected or ascertained non-compliance with LT4 or PPI therapy;
- E2. subject requiring changes of levothyroxine dose<sup>1</sup>;
- E3. use of over-the-counter (OTC) PPIs, unless directed by the prescribing physician<sup>2</sup>;

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<sup>1</sup> Should a patient require LT4 dose adjustment at screening visit, it will be possible to re-screen the patient until TSH normalization under the new dose (see also section 7.2). Should a patient require LT4 dose adjustment at baseline visit, the subject will be excluded.

<sup>2</sup> Use of OTC PPIs will only be allowed if the patient is using an OTC PPI chronically as directed by his/her prescribing physician, and chronic prescription can be appropriately documented (copy of the documentation to be collected and kept in the patient's file)

<sup>3</sup> Appropriate methods are implants, injectables, combined oral contraceptives, IUDs, sexual abstinence or vasectomised partner.

- E4. history of malabsorption or history of gastric bypass surgery, short-gut syndrome, inflammatory bowel disease and other conditions of the gastrointestinal tract that may affect drug absorption (e.g. celiac disease)<sup>4</sup>;
- E5. multiple co-morbidities (e.g. cardiac heart failure, active arrhythmia or history of arrhythmia, particularly atrial fibrillation, uncompensated diabetes mellitus, uncorrected adrenal insufficiency, seriously compromised hepatic, renal and/or respiratory functions)<sup>4</sup>;
- E6. neoplastic pathology, active or in remission for less than 5 years (excluding the basic thyroid pathology)<sup>4</sup>;
- E7. terminal condition;
- E8. parenteral or assisted enteral feeding;
- E9. presence of any medical condition or other circumstances which would significantly affect the safety of the subject or decrease the chance of obtaining reliable data, achieving study objectives or completing the study<sup>4</sup>;
- E10. history of alcoholism, drug abuse or psychiatric diseases that could invalidate the informed consent or limit the subject compliance with protocol requirements<sup>4</sup>;
- E11. pregnant (positive urine pregnancy test at screening or baseline visits) or breast-feeding subject or subject planning a pregnancy in the next months;
- E12. known hypersensitivity to the ingredients of the preparation involved in the study<sup>4</sup>;
- E13. use of forbidden concomitant medications (see [section 6.5](#))<sup>4</sup>;
- E14. regular consumption of soy and soy derivatives, cotton seed meals, walnuts, and dietary fibers;
- E15. participation in other clinical studies during the 3 months prior to screening;
- E16. presumption of poor reliability/cooperation;
- E17. any reason which, in the opinion of the Investigator, would prevent the subject from participating in the study.

#### 5.4 Withdrawal of subjects

Participation may be discontinued for any of the following reasons:

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<sup>4</sup> Checked by medical history



- voluntary subject withdrawal for any reason;
- at the Investigator's discretion (reason should be specified);
- if an adverse event (including worsening of concomitant illness) develops, which is considered by the Investigator as incompatible with the continuation of the study;
- if the administration of a drug which is not permitted according to the exclusion criteria is necessary (this should be discussed between the Investigator and the Sponsor);
- failure to comply with the requirements of the protocol or significant protocol deviation (e.g. inclusion error, evidence of non-compliance with exclusion/inclusion criteria arisen during the study, subject misses study visits or/and is not compliant with drugs intake, etc.);
- if a pregnancy develops;
- lost to follow-up;
- patient death;
- if LT4 dose adjustment is required upon receipt of baseline (V2) laboratory results and before any control visit (interim or unscheduled) is performed;
- if PPIs dose adjustment outside the allowed range is necessary or if PPIs are discontinued.

Subjects who withdraw or are withdrawn from the study after inclusion in the Tirosint® treatment phase (V2) will not be replaced. Subjects who withdraw or are withdrawn from the study before inclusion in the Tirosint® treatment phase (during the run-in phase) will be considered as screening failures.

See section 7.4 for the assessments to be performed in case of early withdrawal.

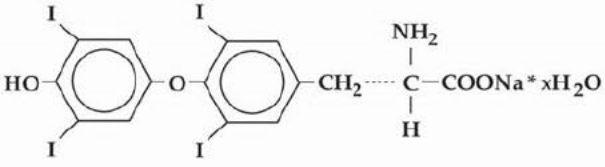
## 5.5 Premature termination

IBSA as the Sponsor has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under treatment at the time of termination must undergo a final examination which must be documented.

IBSA as Sponsor should submit notification of premature termination or temporary halt to IEC and CA, providing justification for the decision.

## 6 TREATMENTS

### 6.1 Investigational / Non Investigational Medicinal Product (IMP/NIMP)

STUDY MEDICATION CHARACTERISTICS	
Generic/Trade Name:	Tirosint®
Chemical Name:	L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine sodium]
Structural Formula and Molecular Weight (MW):	
Name of Manufacturer/Marketing Authorization Holder (MAH):	Empirical formula: C <sub>15</sub> H <sub>10</sub> I <sub>4</sub> N NaO <sub>4</sub> • H <sub>2</sub> O  MW: 798.86 g/mol (anhydrous)  Manufactured by: <div style="background-color: black; width: 150px; height: 20px; margin: 5px auto;"></div>
Formulation:	Distributed by:  IBSA Pharma Inc Parsippany, NJ 07054, USA
Strength:	capsule  13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 mcg
Dose regimen:	once daily
Route of administration:	oral
Storage Conditions:	Store at 25°C (77°F); excursions permitted to 15°-30°C (59-86°F) [See USP Controlled Room Temperature]. TIROSINT capsules should be protected from heat, light and moisture

## 6.2 Dosage and administration

The following strengths of Tirosint® (levothyroxine sodium) capsules are available by prescription on the market: 13, 25, 50, 75, 88, 100, 112, 125, 137, 150 mcg. The 175 and 200 mcg strengths have been recently authorized, but may not be supplied until they will become available on the market. The strengths necessary to obtain the dosage schedule between 88 and 250 mcg/day will be provided. Where the strength is not available, doses higher than 150 mcg will be obtained by combining different strengths (e.g. 100+75 mcg capsules =175 mcg, 100+100 mcg capsules =200 mcg, 125+100 mcg capsules =225 mcg, 150+100 mcg capsules =250 mcg). Additional or intermediate daily dosages may be obtained by using also the lowest strengths, between 13 and 50 mcg.

Different batches may be provided during the course of the study.

At screening the Investigator will accurately report the information regarding LT4 product and dose, as well as PPI product and dose with which the patient is on therapy in the Case Report Form (CRF).

During the first 4 to 6 weeks of the study (run-in phase), patients will continue taking their levothyroxine and PPI medications as per prescription, at their current dose.

Upon baseline visit and inclusion, patients will be switched to Tirosint® capsules at the same dose under which he/she is currently being treated and will remain on Tirosint® for 12±1 weeks. Each patient will be dispensed 2 boxes (60 capsules) of the appropriate Tirosint® strength at Visit 2 and 2 boxes (60 capsules) of the appropriate Tirosint® strength at Visit 3. These should allow treatment for 6 weeks plus a reserve in case of delay of the subsequent visit. Additional boxes may be dispensed in case the dosing schedule requires combination of several strengths (for instance, in case of daily dose of 200 mcg, 4 boxes of 100 mcg will be dispensed). The Investigator will make sure that the patient is given enough supplies for treatment up to the next visit.

At the same time, patients will continue their regular intake of Rx PPI, throughout the whole study duration, according to prescription.

Tirosint® will be taken as a single daily dose in the morning, on an empty stomach, one-half to one hour before breakfast, according to labelling. All subjects will separate their LT4 by at least 4 hours from any drug known to interfere with LT4 absorption (e.g. iron and calcium supplements, see section 6.5) and by at least 1 hour from foods that are known to interfere with LT4 absorption.

The patients will continue intake of PPI according to their individual prescription and habits.

Patients will remain on their pre-screening dose (both for LT4 and for PPI) throughout the whole study duration.



No LT4 dose adjustments will be allowed during the whole study, unless TSH levels > 10 or < 0.01 mIU/L are measured, which require immediate dose adjustment of LT4. In particular:

- If TSH levels > 10 or < 0.01 mIU/L are measured during the baseline visit the subject will drop-out, because pre- and post-switch comparisons at the same dose would not be possible.
- If TSH levels > 10 or < 0.01 mIU/L are measured during control visits (interim or unforeseen), the dose will be adjusted and the subject will remain in the study. To the purpose of the efficacy evaluation in such cases reference is made to section 11.3.

The Investigator can adjust the LT4 dose for a patient with TSH levels < 10 or ≥ 0.01 mIU/L, if this is considered necessary for the safety of a patient. The reason should be appropriately documented.

Changes in the dose of PPI are acceptable during the study provided that the dose remains ≥ 20 mg/day for omeprazole, esomeprazole and rabeprazole, ≥ 15 mg/day for lansoprazole, ≥ 30 mg/day for dexlansoprazole, and ≥ 40 mg/day for pantoprazole. If the newly prescribed dose falls outside this range or if the therapy with PPI is interrupted, the subject will drop out of the study.

Any changes will be described in the CRF.

### **6.3 Packaging and labeling**

Tirosint® will be supplied in its original packaging material, as boxes of 30 capsules, consisting of 3 blisters with 10 capsules each. The dosage strength on each box is clearly identified in several locations, and is associated with a distinct colour. The colour of the circles on the blister is the same colour as on the box. Each blister pack contains 10 capsules placed in individual cavities labeled with the dosage strength, the product name (TIROSINT), and an abbreviation for the day of the week on which the capsule is taken.

The individual cavities containing the drug should not be separated from the intact blister as important information may be lost (i.e., manufacturer/distributor names, distributor contact phone number, lot number, and expiration date), and the individual capsules should not be removed from blister packaging until ready to use.

Because it is not possible to know in advance which strength of Tirosint® will be administered to each patient, no individual subject supplies will be prepared.

Study specific information will be reported in an additional label without covering the original information.

Study-specific labeling of Tirosint® will be performed by IBSA Institut Biochimique SA, Switzerland, in accordance with Good Manufacturing Practices (GMPs) requirements, and with local regulations and will report at least the following information:



- Sponsor's name and contact information
- Study N°
- Subject N° (blank)
- Date of dispensing (blank)
- "For clinical trial use only."

At the time of dispensing, the Investigator or designee will be required to write on the label of the box of the IMP the Subject N.<sup>5</sup> and the date of dispensing.

Investigators' name, address and telephone number (main contact information on the product and clinical trial) will be provided separately on a Patient's Card, that the Investigator or designee will give to the patients at the time of dispensing, with the instruction to keep it in their possession at all times.

Labels will have a tear-off part to allow for proper tracking of dispensing.

#### **6.4 Storage and accountability**

After receipt of the drug supplies (IMP), the Clinical Investigator, his/her deputy or the Pharmacist will conduct an inventory and subsequently fill-in and sign the Drug Receipt Form. Drug inventory and drug accountability records will be kept by the Investigator, his/her deputy or the Pharmacist.

Any particular storage condition will be rigorously followed (see section 6.1).

The Investigator and/or Pharmacist will keep study drugs in a pharmacy or a locked and secure storage facility, accessible only to those individuals authorized by the Investigator and/or Pharmacist himself.

At the conclusion of the study, a final study drug inventory for IMP will be performed and any unused drug will be returned together with a Drug Return Form accurately filled-in and signed by the Clinical Investigator or his/her deputy or by the Pharmacist. If any supplies are missing, this must be indicated together with an explanation for the discrepancy.

At Visit 2, the Investigator will select the appropriate strength of IMP to be provided to the patient, he/she will appropriately fill in the Drug Accountability Form with Subject N. and dispensing date, write the Subject N. and the dispensing date on the dispensed boxes, and stick the tear-off parts of the labels in the appropriate space of the Drug Accountability Form.

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<sup>5</sup> Please notice that the terms Subject N. and Patient N. are considered equivalent.





The Investigator will make sure that the patient is given enough supplies for treatment up to the next visit.

The patients will be instructed to bring back the empty boxes and blisters, as well as the partially used and/or unused boxes and blisters at the next visit. Upon return, the Investigator will record the number of units used and unused and the date of return on the Drug Accountability Form.

At the last visit all the boxes and blisters will have to be collected, being them either used, unused or partially used.

Returned boxes (either used, partially used or unused) will not be discarded, but stored by the Investigator or Pharmacist for drug accountability check purposes, separately from the unused supplies. Boxes that have been dispensed to a patient and are returned unused cannot be re-dispensed to another patient, but will be stored by the Investigator or Pharmacist together with the used boxes.

## 6.5 Concomitant medications and study restrictions

All concomitant medications (prescription and OTC) taken in the time frame from screening to the end of the study will be recorded in the Concomitant Medication section of the CRF. Multivitamins and other supplements will also be recorded.

Many drugs can affect thyroid hormone pharmacokinetics and may alter the therapeutic response to LT4 (IBSA Pharma Inc 2018). Unless otherwise specified, **the following medications will be forbidden throughout the study period** (from screening to final visit). If administration of such medication becomes necessary during the course of the study, subject withdrawal or continuation should be discussed between the Investigator and the Sponsor.

Thyroid hormones other than those involved in the study, e.g. triiodothyronine (LT3), LT4+LT3 combinations or desiccated thyroid extracts.

Drugs That May Alter Hepatic Metabolism of T4 (Hypothyroidism):

- Phenobarbital
- Rifampin

Potential impact: Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements.

Drugs That May decrease conversion of T4 to T3:

- Beta-adrenergic antagonists (e.g., Propranolol > 160 mg/day)
- Glucocorticoids (e.g., Dexamethasone  $\geq$  4 mg/day)
- Other: Amiodarone

Drugs That May Alter T4 and Triiodothyronine (T3) Serum Transport Without Affecting Free Thyroxine (FT4) Concentration (Euthyroidism):

- Clofibrate (Atromid-S)
- Heroin / Methadone
- 5-Fluorouracil
- Mitotane
- Tamoxifen
- Steroids (estrogen-containing oral contraceptives, oral estrogens, androgens / anabolic steroids, glucocorticoids)<sup>6</sup>
- Asparaginase
- Slow-Release Nicotinic Acid
- Salicylates (> 2 g/day)
- Other drugs (Carbamazepine, Furosemide > 80 mg IV, Heparin)
- Hydantoins (e.g. phenytoin)
- Non-Steroidal Anti-inflammatory Drugs (Fenamates)

Drugs that may decrease T4 absorption, which may result in hypothyroidism:

- Antacids (Aluminum & Magnesium Hydroxides, Simethicone)
- Sucralfate (Carafate)
- Orlistat (Alli, Xenical)

Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism.

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<sup>6</sup> Oral contraceptives, estrogen/progestogen replacement therapy and testosterone replacement, as well as glucocorticoids are allowed if at stable doses throughout the entire study duration (from screening to final visit).

### Antidepressant Therapy

Concurrent use of tricyclic (e.g., amitriptyline) or tetracyclic (e.g., maprotiline) antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and central nervous system stimulation. Levothyroxine may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.

### Tyrosine-Kinase Inhibitors:

Concurrent use of tyrosine-kinase inhibitors such as imatinib may cause hypothyroidism.

### **Levothyroxine should be administered at least 4 hours apart from these agents:**

- Calcium Carbonate
- Ferrous Sulfate
- Bile Acid Sequestrants (Colesevelam, Cholestyramine, Colestipol)
- Ion Exchange Resins (Kayexalate, Sevelamer)

### **Caution should be considered in the following cases:**

- **Antidiabetic Therapy:** Addition of levothyroxine therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control, upon switch to Tirosint.
- **Oral Anticoagulants:** levothyroxine increases the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant may be warranted with correction of the hypothyroid state or when the levothyroxine dose is increased. Closely monitor coagulation tests to permit appropriate and timely dosage adjustments upon switch to Tirosint.
- **Digitalis Glycosides:** levothyroxine may reduce the therapeutic effects of digitalis glycosides. Serum digitalis glycoside levels may decrease when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides.
- **Ketamine:** Concurrent use of ketamine and levothyroxine may produce marked hypertension and tachycardia. Closely monitor blood pressure and heart rate in these patients.

- **Sympathomimetics:** Concurrent use of sympathomimetics and levothyroxine may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.

## **Foods**

Consumption of certain foods may affect levothyroxine absorption thereby necessitating adjustments in dosing. Soy and soy derivatives, cotton seed meal, walnuts, and dietary fiber may bind and decrease the absorption of levothyroxine sodium from the gastrointestinal tract. Grapefruit juice may delay the absorption of levothyroxine and reduce its bioavailability. Regular consumption of this food is therefore an exclusion criterion and it is prohibited during the whole study period (from screening to last visit). Occasional consumption is allowed.

## **Biotin**

Biotin has been reported to interfere with some immunoassays using a streptavidin-biotin complex. In the frame of the laboratory tests performed in the present study, the TSH assay (primary parameter of evaluation) is not using a streptavidin-biotin complex and is therefore not affected by high levels of circulating biotin. FT4 assay is negligibly affected (2%) by high levels of circulating biotin. SHBG is affected by high levels of circulating biotin. For this reason, information on the use of biotin should be collected in the CRF and patients should be advised to possibly interrupt biotin intake for 2 days before the visits.

## **6.6 Precautions/Overdosage**

Precautions and overdosage are described in the labelling of the product.

The patients are already under treatment with levothyroxine and with PPIs at stable doses, therefore an evaluation of the precautions for use has already been done at the time of prescription and during the periodic monitoring of the diseases.

Since the patients are routinely under treatment with levothyroxine and PPIs, the risk of overdosage should be minimal.

## **6.7 Treatment allocation and randomisation procedures**

The study is a non-randomized study.

## 6.8 Emergency code and unblinding procedures

This is an open study; therefore unblinding procedures are not needed.

## 7 STUDY PROCEDURES

### 7.1 Overall study schedule

Study schedule is summarized at page 11.

### 7.2 Screening/Inclusion

#### *Visit 1 - Day -28/-42 (Screening Visit)*

The screening procedures (Visit 1) will be performed between 4 and 6 weeks prior to inclusion.

Patients will be screened by endocrinologists.

Subjects should come to the clinical center holding their morning dose of LT4 and possibly bringing with them the box of the LT4 and PPI that they are on therapy with for a visual check by the Investigator. They will be asked to sign the Informed Consent Forms before the start of any screening procedures.

The screening visit will include:

- informed consent<sup>7</sup>;
- demography;
- medical and medication history;
- general physical examination (including neck exam, cardiac exam, and respiratory exam);
- body weight (BW), height;
- vital signs (blood pressure [BP], heart rate [HR]);
- check of inclusion/exclusion criteria;
- blood sampling for thyroid function tests (TSH, FT4, FT3, TT3);

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<sup>7</sup> The date of the informed consent signature may also precede the date of the screening visit.



- urine pregnancy test (in female subjects of childbearing potential);
- diary dispensing;
- instruction of the patient on how to complete the diary and how to comply with the study requirements (i.e. drugs intake, study restrictions, etc.).

The screened subjects will receive consecutively a Subject N. starting from 001 and preceded by a two-digit code identifying the center (where 01 = [REDACTED]). Should additional centers be involved, these will be identified as 02, 03, 04, etc.) (i.e. 01-001, 01-002, etc. and 02-001, 02-002, etc.), that they will retain from the first Screening Visit until the Final Visit.

Clinical signs/symptoms of hypothyroidism or hyperthyroidism (e.g. palpitations) reported by the patient at the screening visit, if clinically significant, will have to be recorded as medical history in the CRF.

The current LT4 product and dose, as well as the current PPI product and dose will be accurately recorded in the CRF, possibly checking with the medication box/bottle if the patient has brought them with him/her.

Subjects complying with inclusion/exclusion criteria will enter a run-in period, during which they will remain on their current dose of LT4 tablets and will keep taking their PPI as prescribed. Patients will have to fill in a diary reporting the daily intake of LT4 and PPI.

The date of Visit 2 will be scheduled and patients will be asked to come to the clinical center for the next visit, fasting and holding their morning dose of LT4, and bringing with them their diary and possibly the box/bottle of the LT4 and PPI that they are on therapy with.

#### *Re-screenings*

Should the patient require LT4 dose adjustment, it will be possible to re-screen the patient until TSH normalization under the new dose. During re-screenings (not more than 2 re-screenings are allowed) the Investigators should check thyroid function tests (i.e. TSH, FT4, FT3, TT3) at appropriate time intervals (as per [IBSA Pharma Inc 2018](#), 6-8 weeks after dose is changed), as well as the safety of the subjects (adverse events and concomitant medications). Diary will be collected and checked to verify compliance with LT4 and PPI and new diary/ies will be provided to cover the overall screening period. When re-screenings are necessary, the time frame between first screening and baseline visit will be extended, provided that the time interval between re-screening and V2 is kept within -28/-42 days, and that the overall screening period does not exceed 4 months.



### 7.3 Treatment phase

#### *Visit 2 - Day 1 (Baseline and Inclusion Visit)*

Four to six weeks later, the patients will report to the clinical center in the morning at around 8h00 ± 2h, fasting for at least 10 hours and holding their daily dose of levothyroxine and bringing with them their diary and possibly the box/bottle of the LT4 and PPI for:

- adverse events (AEs) and concomitant medications;
- body weight (BW);
- diary collection and check to verify compliance with LT4 and PPI;
- re-check of inclusion/exclusion criteria;
- urine pregnancy test (in female subjects of child bearing potential);
- blood sampling for thyroid function tests (TSH, FT4, TT4, FT3, TT3);
- serum laboratory tests: creatine phosphokinase (CPK), sex-hormone binding globulin (SHBG), ferritin, angiotensin-converting enzyme (ACE), and lipid panel (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], very low-density lipoprotein cholesterol [VLDL-C], triglycerides [TG]).
- Tirosint® dispensing;
- diary dispensing;
- remind the patient how to complete the diary and how to comply with the study requirements (i.e. drugs intake, study restrictions, etc.);
- fill in and send the Declaration of Inclusion.

The new onset or the worsening of clinical signs/symptoms of hypothyroidism or hyperthyroidism (e.g. palpitations) reported by the patient, if clinically significant, will have to be recorded as adverse events.

Any changes in the concomitant medications, including the PPI product and/or dose will be recorded in the CRF.

If the subject brings them, the LT4 and PPI box/bottle will be checked to verify changes from the previous visit.

Subjects who are still judged eligible will be dispensed sufficient amount of Tirosint® capsules for treatment up to Visit 3.

The date of Visit 3 will be scheduled and subjects will be asked to come to the clinical center for the next visit, holding their morning dose of LT4, and bringing with them their diary, the box of the PPI that they are on therapy with and the unused, used and partially used boxes and blisters of Tirosint®.

As far as possible, the subjects should begin taking Tirosint the same day of V2, after blood sampling has been performed. The day of first intake of Tirosint will be considered as Day 1 of the study.

***Visit 3 - Day 42±7 (Interim visit)***

Halfway through the treatment period (i.e. 35-49 days after V2), the patients will report to the clinical center in the morning, holding their daily dose of levothyroxine and bringing with them their diary as well as the unused, used and partially used boxes of Tirosint, and the box/bottle of the PPI, and will undergo:

- adverse events (AEs) and concomitant medications;
- blood sampling for thyroid function tests (TSH, FT4, FT3, TT3) for safety check;
- Tirosint® capsules return and count to check compliance;
- diary collection and check to verify compliance with LT4 and PPI;
- Tirosint® dispensing;
- diary dispensing;
- remind the patient how to complete the diary and how to comply with the study requirements (i.e. drugs intake, study restrictions, etc.).

The new onset or the worsening of clinical signs/symptoms of hypothyroidism or hyperthyroidism (e.g. palpitations) reported by the patient, if clinically significant, will have to be recorded as adverse events.

Any changes in the concomitant medications, including the PPI product and/or dose will be recorded in the CRF.

If the subject brings it, the PPI box/bottle will be checked to verify changes from the previous visit.

All the used boxes of Tirosint® will be collected by the Investigator, pills will be counted for check of compliance and drug accountability, and the boxes will be stored by the Investigator or Pharmacist separately from unused supplies. Leftover pills cannot be re-dispensed.

Patients will be dispensed sufficient amount of Tirosint® capsules for treatment up to Visit 4.



The patients will be asked to take their morning LT4 dose only after blood sampling and will continue taking the study medications at the prescribed dose.

The date of Visit 4 will be scheduled and patients will be asked to come to the clinical center for the next visit, fasting and holding their morning dose of LT4, and bringing with them their diary, the box/bottle of the PPI that they are on therapy with and the used, partially used, and unused boxes of Tirosint®.

#### **7.4 Final visit**

##### ***Visit 4 – Day 84±7 (Final visit)***

Twelve weeks after treatment start, the patients will report to the clinical center in the morning at around 8h00 ± 2h, fasting for at least 10 hours and holding their daily dose of levothyroxine and bringing with them their diary as well as the unused, used and partially used boxes of Tirosint®, and the box/bottle of the PPI, and will undergo:

- adverse events (AEs) and concomitant medications;
- general physical examination (including neck exam, cardiac exam, and respiratory system);
- body weight (BW);
- vital signs (BP, HR);
- 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);
- Tirosint® capsules return and count to check compliance;
- diary collection and check to verify compliance with LT4 and PPI.

The new onset or the worsening of clinical signs/symptoms of hypothyroidism or hyperthyroidism (e.g. palpitations) reported by the patient, if clinically significant, will have to be recorded as adverse events.

Any changes in the concomitant medications, including the PPI product and/or dose will be recorded in the CRF.

If the subject brings it, the PPI box/bottle will be checked to verify changes from the previous visit.

All the unused, used and partially used boxes of Tirosint® will be collected by the Investigator, pills will be counted for check of compliance and drug accountability, and the boxes will be stored by the Investigator or Pharmacist separately from unused supplies.

For patients completing the study as per protocol, this will correspond to the Final Visit.

#### *Study discontinuation*

If a patient drops out of the study or in case of study discontinuation (i.e. after inclusion in the Tirosint® treatment phase), the Investigator will attempt to perform a Final Visit, including at least the following assessments for safety purposes:

- adverse events (AEs) and concomitant medications;
- general physical examination (including neck exam, cardiac exam, and respiratory exam);
- body weight (BW);
- vital signs (BP, HR);
- blood sampling for thyroid function tests (TSH, FT4, TT4, TT3, FT3);
- serum laboratory tests: CPK, SHBG, ferritin, ACE, and lipid panel (TC, HDL-C, LDL-C, VLDL-C, TG);
- Tirosint® capsules return and count to check compliance;
- diary collection and check to verify compliance with LT4 and PPI.

If the subject brings it, the PPI box/bottle will be checked to verify changes from the previous visit.

The Investigator will fill in a Study Termination Form in the CRF to explain the reason for study discontinuation.

#### **7.5 Follow-up (if applicable)**

No follow-up visits are foreseen, unless required by adverse events developing during the study (see section 10.1). See also section 7.6.

#### **7.6 Unscheduled visits (if applicable)**

Unscheduled visits may be performed during the study or after the end of the study if judged necessary for the safety of the patient. See also section 7.5. The appropriate section(s) of the CRF will be completed.

### **8 OTHER STUDY MATERIAL**

Beside the study medications, the Sponsor will provide at least the following study material:



- Final version of the study protocol
- Investigator's File
- Case Report Forms (CRFs)
- Subject's Diaries
- Patient Information Sheet and Written Informed Consent Forms
- Serious Adverse Event Forms and Pregnancy Forms
- Material for serum samples collection and shipment
- Boxes for serum samples freezing and storage (second aliquot)

Additional forms may be provided, if necessary to collect study data.

## **9 MEASUREMENT OF EFFICACY AND SAFETY VARIABLES**

### **9.1 Primary Efficacy variables**

The primary efficacy variable will be the serum levels of TSH.

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

Samples of peripheral venous blood will be taken from the patient at each visit at around 8h00 ± 2h (fasting conditions will be required at Visits 2 and 4). LT4 administration will be delayed until after sample collection.

Approximately between 13 and 23 mL of whole blood will be collected at each visit. The exact amount to be collected at each visit will be defined in the laboratory Investigator's manual. Blood may be drawn and processed by the clinical center main laboratory.

Serum will be collected and divided into 2 aliquots:

1. the first aliquot (S1) (all available volume except 1 mL) will be sent immediately (on the same day) to the central laboratory for analysis, and will be analyzed as per their current methods immediately after. Results will be provided to the Investigator as soon as available. If, for any reasons, shipment on the same day is not possible, aliquot S1 will be stored by the clinical center at  $\leq -20^{\circ}\text{C}$  and shipped to the central laboratory within 7 days.
2. the second aliquot (S2) (1 mL) will be stored by the clinical center at  $\leq -20^{\circ}\text{C}$  as a back-up sample, to be analyzed in case something happens to S1 aliquot or they may





be analyzed at the end of the study, in case it is deemed necessary to repeat the analyses in a single run. Samples will be stored until otherwise requested by the Sponsor of the study.

The total amount of blood that will be collected over the whole study duration should not exceed 100 mL.

Validated kits will be used for the analyses.

Individual patients kits for blood sampling and serum collection specific for each visit will be provided by the laboratory. Further details will be specified in a dedicated Investigator's Manual.

No analyses other than those indicated in the informed consent form will be performed unless a new informed consent and a new approval from the Ethical Committee is obtained. Patients may ask to destroy their own samples at any time.

Record of samples transfer or destruction will be kept in the Investigator's File. Copy will be provided to the Sponsor.

## **9.2 Secondary Efficacy variables**

The secondary efficacy variables will be the serum levels of FT4, TT4, FT3, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel.

Serum levels of FT4, FT3 and TT3 will be measured at screening visit, 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).

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.

Please refer to section [9.1](#) for methodological details.

## **9.3 Safety variables**

Adverse events will be recorded at each visit. In addition, a physical examination including vital signs, neck exam, cardiac exam and respiratory exam will be performed at screening and final visits. Body weight will be recorded at screening, baseline and final visit.

## **10 ADVERSE EVENTS DESCRIPTION & REPORTING**

Adverse event definitions and classification are reported in [Appendix I](#).




All the occurred adverse events (AEs), independently from their classification, must be reported on the CRF in the “adverse event” section.

A dedicated form is required for the reporting of the Serious Adverse Events (SAE form).

All the Serious Adverse Events (SAE) which occur during the clinical trial, independently of their causal relationship, must be reported immediately (i.e. within 24 hours after first knowledge) by fax or email to:



The collection period of AEs/SAEs for each subject starts from the signature of the informed consent until the end of the study and/or the follow-up planned period.


When the Investigator has received knowledge of an SAE, he/she should fulfill a SAE form (Type of report: initial) with the support of the **Study Coordinator/Monitor**, if necessary, and send it to  by fax or email as soon as possible but within 24 hours.

The preliminary notification should include, at least, this minimum information:

- 1) EUDRACT (if applicable) and protocol numbers;
- 2) Patient’s identification (initials - only when applicable according to local regulations- screening/randomization number, date of birth, gender), relevant medical history;
- 3) SAE description and its onset;
- 4) Investigator’s causality assessment on the event relationship with the study medication;
- 5) IMP batch N°, first admin- and last admin before SAE, if code broken – when applicable;
- 6) Specific treatment of the SAE;
- 7) Investigator: name, address, phone number.

SAEs must be monitored until resolution or acceptable stabilization in the event of chronicity.

In case of death, the Investigator will be requested for forwarding the autopsy report, if available.

When the investigator receives additional information regarding the initial SAE, he/she should fill in a new SAE form and tick the “Follow Up” box and fax or email it within 48 hours to the .





All SAEs, qualified for the reporting to FDA, will be submitted to FDA by IBSA or its delegate according to the post-marketing pharmacovigilance reporting requirements, within **15 calendar days** from IBSA's first knowledge.

Follow-up reports will be reported within 15 calendar days of receipt of new information or as requested by FDA.

The clock for expedited reporting (day 0) starts as soon as the information containing the minimum reporting criteria has been received by IBSA.

A list of all AEs classified as "non-serious" will be collected at the time of monitoring visits and transmitted to IBSA and will not need to be submitted to the FDA.

### **10.1 Follow-up**

Adverse events not related to the study drug or study procedures will be followed up until final visit (V4). SAEs and adverse events for which relationship to the study drug or to the study procedures cannot be excluded will be followed up until resolution or stabilization, or until the Investigator judges safe to discontinue follow-up (to be justified in the CRF).

Planned medical procedures (not only surgical) which are not taken as an action to an event having occurred during the study, will not be followed-up and should not be considered as SAE, if already planned before the inclusion.

### **10.2 Pregnancy**

Non-pregnant women will be enrolled in this study. Adequate and continuative contraceptive measures until the end of the study are requested, if not in menopause (see section 5.2). Moreover, for fertile women a urine pregnancy test will be performed at screening and baseline visits, to exclude pregnancy.

When the Investigator has received knowledge of exposure during pregnancy, the pregnancy form should be fulfilled and forwarded to [REDACTED] within 24 hours from the first knowledge, by fax or email to:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The pregnancy should be followed until delivery.

The outcome section of pregnancy form will be completed as soon as the investigator has knowledge of the pregnancy outcome. If it meets the criteria for immediate classification of a





SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the Investigator should follow the procedure for reporting SAEs.

If the subject becomes pregnant during the study, she will drop out of the study.

If the pregnancy is discovered before taking any dose of study drug or of the background medication, the pregnancy does not need to be reported; it is only required that the subject is immediately withdrawn from the study.

## **11 DATA MANAGEMENT AND STATISTICAL ANALYSIS**

### **11.1 Data Management**

Data management will be performed by [REDACTED], under the responsibility of Data Management and Statistics Manager.

#### *11.1.1 CRF*

Specific CRFs for the collection of the data pertaining to this clinical trial will be provided to the Investigator(s), who is responsible for ensuring that the data required are carefully reported. CRFs will be designed in order to act as a reminder both as far as the timing and the nature of the data to be collected are concerned. The initial page will specify how to fill them in, in agreement with satisfactory regulatory standards.

The original CRF will be retrieved by the Sponsor and archived in the Trial Master File at Sponsor premises, while copy will be archived in the Investigator's File (unless the CRF serves as a source document). All CRFs returned to [REDACTED] department will undergo a data-entry procedure in a suitable designed database.

All data coming from central laboratory analysis will be recorded into a suitable database designed directly by the appointed central laboratory.

Specific paper patient diaries for the collection of the data pertaining to trial medications intake will be provided to the patients. The initial page will specify how to fill them in, in agreement with satisfactory regulatory standards.

Copy of the complete handwritten patients' diaries has to be returned to the [REDACTED] and upon receipt data-entry will be performed by IBSA.

#### *11.1.2 Data Management and data Quality Assurance*

The data registered on the CRFs and Patient's Diary of all included subjects will be stored in a suitable database, properly designed by the Data Manager. Queries generated from data entry are issued by the Data Manager according to internal SOP and will be referred to the appropriate hospital/study site personnel, and resolved with assistance of the Study Monitor.



Double data entry (single data entry for diaries) will be performed manually by the Data Capture Personnel.

Data validation checks will be performed electronically for internal consistency and completeness.

Any variables derived during the data management procedures will be calculated and stored in the same data-base as the original variables. All calculations will be documented into the Data Management File.

The Data Manager will perform the data cleaning and data locking in order to prepare the data base for the statistical analysis. The Data Manager is also responsible for sending the database to the appointed statistician.

Details on quality checks and data management procedures to be performed will be further detailed in the Data Management Plan.

## **11.2 Coding Dictionaries**

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

Concomitant medications will be coded using the WHO Drug Dictionary (WHO-DD).

## **11.3 Statistical analysis**

The following describes the statistical analysis as it is foreseen at the time of planning the trial. A detailed statistical analysis plan (SAP) will be described in a separate document to be completed after finalizing the protocol. The statistical analysis plan will be mutually agreed between the appointed statistician and IBSA's Data Management and Statistics Manager.

The plan will be reviewed and may be updated before the start of the statistical analysis, which will start only at the end of data management activities and after the description and discussion of protocol deviations by the clinical team.

The results of the study will be promptly communicated to the Sponsor by the appointed statistician; a draft Statistical Report will be submitted to the Sponsor for comments and agreement before finalization.

### *11.3.1 Sample size*

A sample size of 48 subjects will have 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 will be included in the study (Tirosint® treatment phase).



### *11.3.2 Population for analysis*

The following populations will be considered for the analysis:

**Intent-To-Treat (ITT) population:** all included patients who received at least one dose of the study medication.

**Per-Protocol (PP) population:** 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).

**Safety Population:** all included patients.

All efficacy variables will be analyzed in both the ITTs and PP populations.

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

### *11.3.3 Missing 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 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. Sensitivity analyses based on other imputation methods (e.g. Basal Observation Carried Forward [BOCF], maximum-likelihood based method or others) may also be conducted, and will be fully described in the Statistical Analysis Plan.

### *11.3.4 Protocol deviations*

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

Violations will be classified as major violations or minor violations 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.

### *11.3.5 Interim analysis*

No interim analyses are planned.

#### *11.3.6 Statistical methods*

Data from the CRFs and from the laboratory database will be converted to SAS datasets and will be analyzed using SAS® software version 9.2 for Windows®.

All p-values will be rounded to four decimal places. Statistical significance will be declared if the two tailed p-value is less than 0.05.

Descriptive statistics for continuous variables and frequency counts for categorical variables will be calculated for each variable at every assessment time point.

#### **Primary Efficacy Analysis**

The primary efficacy end-point will be the change in serum levels of TSH at the end of the 12-week treatment period with Tirosint® capsules with respect to baseline.

The serum levels of TSH will be analyzed by means of a repeated measures analysis of covariance on the difference (final vs baseline visit) with basal value as covariate. The 95% confidence interval will be calculated. Additional non-parametric analyses may be performed on the evolution of TSH serum levels as sensitivity analyses.

Baseline variables (e.g. gender, pre-study LT4 product, LT4 dose, PPI product and dose, etc.) may also be used as covariates if appropriate.

#### **Secondary Efficacy Analyses**

The secondary efficacy end-points will be the change in serum levels of FT4, FT3, TT4, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel at the end of each 12-week treatment period with Tirosint® capsules with respect to baseline. The change in serum levels of TSH, FT4, FT3, TT3 at Visit 3 with respect to baseline will also be analysed as secondary efficacy end-points.

Serum levels of FT4, TT4, FT3, TT3, CPK, SHBG, ferritin, ACE level, and lipid panel (TC, HDL-C, LDL-C, VLDL-C, TG) will be analyzed by means of a repeated measures analysis of covariance with basal value as covariate. The 95% confidence interval will be calculated.

Baseline variables (e.g. gender, pre-study LT4 product, LT4 dose, PPI product and dose, etc.) may also be used as covariates if appropriate.

The dose adjustment evaluated in terms of number of patients requiring changes in LT4 daily dose during the treatment period will be described using frequencies and percentages.

Changes in mean LT4 daily dose at the end of the treatment period versus baseline will be analyzed by means of a repeated measure analysis of variance model.

#### **Safety Analyses**

Numbers of patients experiencing Adverse Events (AEs) will be calculated. AEs will be classified using MedDRA categories. Vital signs 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 calculated.

### **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 on the basis of data reported in the Subject's Diary, calculating the percentage of medication taken in relation to the recommended dose and the actual period of treatment (number of doses reported to be taken / number of doses envisaged x 100).

Patients compliance with Tirosint® will also be assessed on the basis of the number of units supplied and the units returned, calculating the percentage of medication taken in relation to the recommended dose and the actual period of treatment (number of doses actually taken / number of doses envisaged x 100).

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 over run-in and treatment periods.

## **12 MONITORING AND ACCESS TO DATA**

### **12.1 Monitoring**

The study will be carried out in accordance with the most recent international GCP guidelines, the FDA CFR 21 part 50, 54, 56 and 312, and the local legislation on the conduct of clinical trials.

IBSA, as Sponsor, has the responsibility of monitoring this study and has delegated this task to a CRO / Study Monitor. Specific contracts have been issued and will be signed by both parties before the study initiation. According to these contracts, the study monitors will use CRO SOPs as reference.

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.

In accordance with the guidelines on GCP and procedures detailed in the study-specific Monitor's Manual or Monitoring Plan, the Clinical Monitor will:

- receive information on the number of visits to be performed and their frequency;
- perform an initiation visit in order to ensure that the site knows all protocol, GCP and local law requirements. During the visit, the Clinical monitor will discuss and clarify all existing doubts about study procedures ensuring that the site is in the best condition to enroll and treat patients.
- Perform regular visits to the center during the trial, approximately every 6 subjects enrolled, with the objective of verifying:
  - Compliance of subjects recruited with the inclusion/exclusion criteria of the protocol;
  - Informed consent;
  - Adherence to all the main procedures specified in the protocol;
  - Adverse event reporting;
  - Recruitment status (number of subjects screened, recruited, ongoing, completed, withdrawals);
  - Drug supply and accountability;
  - Collection, storage and delivery of biological specimens, where appropriate;
  - Source data;
  - Accuracy and completeness of data recorded on the CRFs.
- Perform a final closure visit to check:
  - The final study drug inventory;
  - Resolution of all data queries;
  - Provision for adequate archiving.

The Clinical Monitor will check accuracy and completeness of data recorded performing the on-site source data verification (SDV), in order to clean the data as much as possible without delay. During the on-site monitoring visits, the Monitor will help the Investigator to solve any arisen queries. If needed, at the end of the visit, a list of any outstanding queries will be made and a deadline for the reply will be established.

In order to perform his role effectively, the Clinical Monitor must be given access to source



data which supports data on the CRFs for the study, i.e. appointment books, original laboratory data, etc. The Investigator accepts herewith to allow adequate access to the facilities and to these documents and to ensure that his/her staff dedicates sufficient time to the Clinical Monitor, so that he/she can carry out his/her duties.

More precisely, the following items (at a minimum) have to be collected as source data in the patient's file:

- study code;
- subject's full name, date of birth, sex, weight and height;
- medical history;
- concomitant medications;
- date of inclusion and subject identification (Subject number);
- date of subject's written informed consent;
- study drug administration (e.g. start and end of study treatment);
- date of the visits;
- AEs and SAEs occurring during the study;
- date of withdrawal and reason;
- laboratory analyses results;
- urine pregnancy results.

Specific items required as source documents will be reviewed with the Investigator before the trial. Subject's diary and evaluation form at site will be considered source documents.

## **12.2 Quality Control and Quality Assurance**

The Investigator is responsible for ensuring that the clinical data required by the study protocol are carefully reported in the CRFs. The data entered in the CRF (in English language) must also be present in the source documents of the subject at the investigational centre.

All study documentation and results may be reviewed by the Quality Assurance Units of IBSA or delegates and/or local and foreign Regulatory Authorities. The Investigator accepts herewith to give access to the facilities and to the source data upon request. The Investigator must also permit trial monitoring, audits, EC review or regulatory inspections.





## **13 ETHICAL AND REGULATORY ASPECTS**

### **13.1 Declaration of Helsinki**

The study will be conducted in accordance with the Declaration of Helsinki (1996) and its amendments.

### **13.2 Regulatory requirements**

Application to the National Regulatory Authorities for approval of this study is not applicable. According to 21 CFR 312.2(b), indeed a clinical investigation of a marketed drug is exempt from the IND requirements if all of the following criteria are met:

(1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labelling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.

### **13.3 Ethical Committee approval**

The protocol will be submitted to the Local Ethical Committee/Institutional Review Board (EC/IRB) for the approval, together with the Information Sheet for informed consent and any other document required by the EC/IRB. An approval document from the EC/IRB must be received with specific reference to this protocol (and unconditional approval) before starting the study and will be enclosed in the final report.

Any subsequent amendment and/or relevant information (e.g. serious adverse events) that comes to light after EC/IRB approval will be sent to the EC/IRB, according to local requirements.





IBSA will ensure that study drug is not dispatched to the centers before the copy of the approval has been obtained. Selection of the patients will not start before the approval of the EC/IRB has been obtained.

#### **13.4 Protocol Amendments**

Neither the Investigator nor IBSA will modify or alter this protocol without first obtaining the agreement of the other part.

A new approval from the EC/IRB must be obtained before implementation of any substantial amendment, except when it is necessary to eliminate apparent immediate hazard to the subject.

All agreed protocol substantial amendments must be clearly recorded, signed and dated by IBSA and the principal Investigator (Coordinating investigator in case of multicenter trials).

Any non-substantial amendment should be written by IBSA and its final version has to be signed at least by the principal investigator(s) as well as by the responsible IBSA R&D staff (e.g., project manager, R&D director). The original document will be filed in the Study Master File at IBSA headquarters.

#### **13.5 Written informed consent**

In seeking informed consent, the Investigator will inform the subject that participation to the trial is voluntary and that refusal will not lead to loss of any benefit or prejudice the relationship with the physician in any way. Furthermore, a statement will be made to the effect that withdrawal from the trial is possible at any moment without having to give a specific reason.

Before enrolment into the trial, each subject will receive a full explanation of the nature and purpose of the study from the Investigator, together with a description of benefits and risks associated with participation; insurance coverage will also be mentioned and related procedures in the event of injury will be explained.

A clear Information Sheet ([Appendix II](#)) covering all important aspects in writing will be given to the subject who will read it and have the opportunity to ask any questions whatsoever.

The subject will be given adequate time for consideration before he/she is requested to sign and date the consent form ([Appendix II](#)).

The signed and dated consent form will be kept by the Investigator in the study file. The subject will receive a copy for future reference.





### **13.6 Insurance**

IBSA will undersign an insurance policy covering subjects who enter the trial. The terms for compensation following drug-induced injuries are included in the Information Sheet for the subject.

Reference to policy number will be included in the patient information sheet.

IBSA will also indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation in excess of those covered by his/her own professional liability insurance providing that the drug was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and the study protocol.

This indemnification does not apply to claims for damages arising out of any act of omission in his/her part or on the part of those under his/her supervision that shall or may amount to negligence in law. The Investigator must notify IBSA immediately upon notice of any claims or lawsuits.

### **13.7 Confidentiality**

Results from the medical examinations and from laboratory tests will be recorded in the subject Case Report Form. All the information obtained during the conduct of the study with regard to the subject's state of health will be regarded as confidential and agreement must be obtained from the subject prior to the disclosure of his/her personal identity to a third party different from authorized personnel of IBSA, and/or Regulatory Authorities.

It is also understood that information from the clinical study will be used by IBSA in connection with a pharmaceutical development and therefore may be disclosed as required to other Clinical Investigators and to Government Authorities.

The Investigator accepts herewith to treat any unpublished information supplied by IBSA as confidential and ensure that confidentiality is kept also by all staff involved in this project. In this respect, no data will be used for presentations at scientific meetings and/or publication in scientific journals without prior agreement with IBSA.

The study will be registered in [clinicaltrials.gov](http://clinicaltrials.gov). This Registry will not include information that can identify patients. At most the Web site will include a summary of the results.

## **14 LOCATION OF DATA**

After completion of the study and analysis of the data, the essential documents (list of documents as per ICH GCP E6, chapter8) will be stored in the Trial Master File, which will be deposited in the Sponsor's archive for storage for at least 10 years according to Swiss regulations, but for 25 years according to new EU regulation.





The essential documents stored in the Investigator's Study File will be archived for at least 10 years. The patients files (hospital charts, source documents and so on) will be stored for the same time period or anyway at least for the maximum period allowed by Hospital/Institution policies, if not differently agreed with IBSA.

Anyway once the 10 years storage period has elapsed, the Investigator should contact IBSA. The Investigator is not allowed to destroy the study related documents without written authorization from IBSA.

<i>Documents</i>	<i>Clinical unit /IF</i>	<i>CRO*</i>	<i>Sponsor/TMF</i>
<i>Confidentiality agreements</i>	<i>original</i>	<i>copy</i>	<i>original</i>
<i>Investigator's Brochure (if applicable)</i>	<i>copy</i>	<i>copy</i>	<i>original</i>
<i>Signed study protocol (°)</i>	<i>original</i>	<i>copy</i>	<i>original</i>
<i>Protocol amendments (°)</i>	<i>original</i>	<i>copy</i>	<i>original</i>
<i>Submission and approval of EC (including members' list)</i>	<i>original</i>	<i>copy</i>	<i>copy</i>
<i>Submission and approval of CA (if applicable)</i>	<i>copy</i>	<i>copy</i>	<i>original</i>
<i>Financial agreements</i>	<i>original</i>	<i>copy</i>	<i>original/copy§</i>
<i>Source/Raw data of subjects, including lab tests and ECG, etc</i>	<i>original</i>	-	-
<i>Insurance contract</i>	<i>copy</i>	<i>copy</i>	<i>original</i>
<i>Certificate of analysis of the test product</i>	<i>copy</i>	<i>copy</i>	<i>original</i>
<i>Drug accountability records</i>	<i>original/copy</i>	<i>copy</i>	<i>original/copy</i>
<i>Signed informed consent form (confidential)</i>	<i>original</i>	-	-
<i>Confidential subjects identification code</i>	<i>original</i>	-	-
<i>Signed CRFs – this comprises electronic CRFs or tools used for electronic remote data capture and electronic or digitalized data, suitably archived.</i>	<i>copy</i>	<i>copy</i>	<i>original</i>
<i>AEs and SAEs forms</i>	<i>Copy</i>	<i>copy</i>	<i>original</i>
<i>Data queries and resolution documents</i>	<i>Copy</i>	<i>copy</i>	<i>original</i>
<i>Curricula vitae of the Investigator and other participants in the study</i>	<i>original</i>	<i>copy</i>	<i>Original/copy</i>
<i>Study staff list and responsibilities</i>	<i>original</i>	<i>copy</i>	<i>copy</i>
<i>Laboratory normal ranges (signed &amp; dated),</i>	<i>Copy</i>	<i>copy</i>	<i>Original/copy</i>
<i>Lab certification of accreditation (central lab)</i>	<i>Copy</i>	<i>copy</i>	<i>copy</i>
<i>Documentation of study drug destruction</i>	<i>copy (°°)</i>	<i>copy (°°)</i>	<i>original</i>
<i>Monitoring reports</i>	<i>copy</i>	<i>copy</i>	<i>original</i>
<i>Final report</i>	<i>copy (synopsis)</i>	<i>copy (synopsis)</i>	<i>original</i>
<i>Randomization list or sealed, single coded envelopes (if applicable)</i>	<i>original(**)</i>	-	<i>original</i>
<i>Study related correspondence</i>	<i>original or copy</i>	<i>original or copy</i>	<i>original or copy</i>
<i>Sealed drug countersamples, sufficient for 3 analytical determinations (§§)</i>	-	-	<i>yes</i>

(°) must be all signed, original copies.

(\*) only in case that the Study Protocol foresees that all or parts of the study activities are managed through a Clinical Research Organization (CRO), other from the Sponsor.

(§) When agreed upon, in case that financial agreements with the Clinical units are managed by the CRO, the Sponsor will retain copies of these financial agreements.

(°°) only if study drug is destroyed at site; an explicit written authorization from the Sponsor must be available.

(\*\*) all, sealed and opened, single coded envelopes will be collected by the study Monitors and returned to the Sponsor once the study is completed.

(§§) samples are stored in the dedicated storehouse of the [REDACTED]



## **15 REPORTING**

A clinical study report (CSR) will be 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 Coordinating Investigator for comments. After receiving the comments, or two months later if no comments are received, a final report will be issued. Any subsequent modification will be considered as an amendment to the final study report. A copy of the synopsis will be provided to the Investigators.

The Investigator'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. At the end of the trial the Sponsor should provide the Ethic Committee and Competent Authorities (if applicable) with a summary of the clinical trial report.

## **16 PUBLICATION POLICY**

The data collected during the study will be the property of the Sponsor, IBSA. IBSA is entitled to publish and/or present any results of this study at scientific meetings, and to submit these clinical trial data to national and international Regulatory Authorities.

The Investigator accepts herewith to treat any unpublished information supplied by IBSA as confidential and ensures that confidentiality is kept also by all staff involved in this project.

Investigator may communicate or publish in scientific journals or other scholarly media with respect to the present study only after allowing for review by the Sponsor. The Sponsor will review the manuscript within 60 days of receipt. Appropriate consideration will be given to the Sponsor's comments and discussion will be held with the Sponsor to solve disagreements. Final authority to disseminate, present and/or publish the scientific material will be at the discretion of the principal investigator(s). Anyway the publication will neither disclose the identity of patients, fully respecting the data protection laws now in force, nor any patent information.

## **17 RESPONSIBILITIES**

The responsibilities of the Investigators are those considered in ICH GCP and FDA CFR §312.60-69.

By signing this protocol the Investigator 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.



The Responsibilities of the Clinical Investigator are anyway summarized and enclosed in [Appendix III](#).

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## **19 APPENDICES**



## **Appendix I**

### ***ADVERSE EVENTS***

#### ***DEFINITIONS AND CLASSIFICATION***

##### ***1. Adverse events (AEs) and their classification***

*Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.*

An adverse event 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.

All adverse events will be classified according to the categories **Serious/Non-Serious, Expected/Unexpected** and **Mild, Moderate** and **Severe**. In addition, the physician responsible for the patient will always be asked to indicate whether a causal relationship exists between the specified event and the study drug.

##### ***2. Serious AE***

**A serious adverse event (SAE) or reaction (SAR) is any untoward medical occurrence or effect that**

at any dose:

- Results in **death**;
- Is **life-threatening**;
- Requires patient **hospitalisation** or **prolongation of existing hospitalization**;
- Results in **persistent or significant disability or incapacity**;
- Results in a **congenital anomaly or birth defect**;
- Is an **important medical event** (i.e. important medical reactions that jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition).



*The term “life-threatening” in the definition refers to an event in which the patient 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.*

Any adverse event which does not fall into the above-described categories is to be defined as **Non Serious**.

### **3. *Unexpected AE***

Any adverse event that is not consistent, in nature, severity or frequency, with the applicable product information (e.g. Investigator’s Brochure (IB) for an unauthorized investigational product or Summary of Product Characteristics (SPC) for an authorized product). Adverse events that are adequately described in the section regarding side effects in the Summary of Product Characteristics (SPC) or in the Investigator’s brochure are to be considered **Expected**.

### **4. *Severity classification***

Regardless of the classification of an adverse event as serious or non-serious, the severity of an adverse event will be rated according to the following definitions:

#### *MILD*

Symptom barely noticeable to study subject and that does not influence performance or functioning. Prescription drug not ordinarily needed for relief of symptom but may be given because of subject’s personality.

#### *MODERATE*

Symptom of a sufficient severity to make the study subject uncomfortable with influence on the performance of daily activities. The subject is able to continue the study, even if treatment for symptoms may be needed.

#### *SEVERE*

Symptom causes severe discomfort. They may be of such severity that the study treatment has to be ended and the subject may be treated for symptoms and/or hospitalized.



It should be noted that a severe adverse event does not have to be serious in nature and vice versa. Contrary to the other two classifications (seriousness and causality), the classification of severity does not have any impact on reporting procedures

## 5. *Causality assessment*

The Investigator responsible for the patient must attempt to identify the cause of each adverse event and its relationship to study drug treatment. Jones' algorithm is used for the causality assessment. The relationship with the study drug will be classified as follows:

### *CERTAIN*

There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

This means: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definite pharmacologically or phenomenologically\* using a satisfactory rechallenge procedure if necessary.

*\*i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon (for instance, 'grey baby syndrome' and chloramphenicol, or anaphylaxis immediately after the administration of a drug that had been given previously). This means that, if this criterion is not met, the relationship between the drug administration and the event onset can never be classified as 'Certain', even in the case of a positive rechallenge.*

### *PROBABLE*

There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

This means: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge).

Re-challenge information is not required for fulfilling this definition.

### *POSSIBLE*





There is some evidence to suggest a causal relationship; however, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

This means: A clinical event, including laboratory test abnormality, with a reasonable time relationship to drug intake or application (topical forms), but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

#### *UNLIKELY*

There is another reasonable explanation for the event occurrence.

This means: A clinical event, including laboratory test abnormality, with a temporal relationship to drug intake that makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

#### *NOT ASSESSABLE*

There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

This means: A report of an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

#### *NOT RELATED*

There is no evidence of any causal relationship.

This means: When sufficient information exists to indicate that the etiology is unrelated to the study drug.





**Adverse Events Form (page 2/2)**

A.E. description	A.E. onset		A.E. stopped		Study Drug last admin. before AE		Seriousness <i>1-2</i>	Severity <i>1-3</i>	Action taken <i>1-7</i>	Outcome <i>1-6</i>	Relationship to treatment <i>1-6</i>	Personnel Initials
	dd/mm/yyyy	hh mm	dd/mm/yyyy	hh mm	dd/mm/yyyy	hh mm						
1)												
2)												
3)												
4)												
5)												
<b>ACTION TAKEN: if given as 2-7 please give details</b>												
<b>OUTCOME: if given as 2-6 please give details:</b>												
<b>RELATIONSHIP: if given as 5-6 please give details:</b>												
<b>SEVERITY: if given as 3 please give details:</b>												

**IMPORTANT: in case of Serious Adverse Event, please inform IBSA immediately by faxing or emailing the SAE Form**

Investigator's signature \_\_\_\_\_

Date: \_\_\_/\_\_\_/\_\_\_





## Serious Adverse Event report (SAE)

### GUIDANCE FOR COMPLETION

The collection period of AE/SAEs for each subject starts from the subject's screening date until the end of the study and/or the follow-up planned period.

All Serious Adverse Events which occur during all periods of the clinical trial, independently of causal relationship, **must be reported immediately (i.e. within 24 hours after first knowledge)** by fax or email to:

████████████████████

████████████████

██████████████████

██

A **Serious Adverse Event (SAE) or reaction (SAR)** is any untoward medical occurrence or effect that at any dose:

- Results in **death**
- Is **life-threatening** (meaning that the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient **hospitalisation** or **prolongation of existing hospitalisation**
- Results in **persistent or significant disability or incapacity**
- Is a **congenital anomaly or birth defect**
- Is an **important medical event** (i.e. important medical reactions that jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition)

Seriousness is not to be confused with severity / maximum intensity (mild, moderate, severe).





Multiple independent SAEs for the same patient which occur *simultaneously* should be described on the same SAE form.

## **Actions in case of SAE/SAR**

When the Investigator has received knowledge of an SAE he/she is expected to proceed as follows:

- 1) Take the appropriate diagnostic and therapeutic measures to minimize the risk for the patient/subject
- 2) Collect evidence for the elucidation of the relationship between SAE and the IMP
- 3) Filling in clearly and legibly the SAE form (Type of report: initial) with all the information requested and fax or email it to IBSA - Drug Safety Unit within 24 hours after first knowledge,
- 4) Contribute to clarification of the cause(s) of the SAE and to the assessment of potential risk by providing any relevant information obtained or requested with respect to the case.

When the investigator receives additional information regarding the initial SAE, he/she should fill in a new SAE form and tick the “Follow Up” box and fax it within 48 hours to the IBSA – Drug Safety Unit

- 5) Complete the AEs form in the CRF

The preliminary notification should include, at least this minimum information:

- 1) EUDRACT (if applicable) and protocol numbers;
- 2) Patient’s identification (initials\* – when applicable according to local regulations-, screening/randomization number, date of birth, gender), relevant medical history;
- 3) SAE/event description and its onset;
- 4) Investigator’s causality assessment on the event relationship with the study medication;
- 5) IMP or batch N°, first admin- and last admin before SAE, if code broken – when applicable;
- 6) Specific treatment of the SAE;
- 7) Investigator: name, address, phone number.





**\*Initials should be never be collected (not even in the SAE Form) in countries where this is not permitted**

## **Causality assessment**

The investigator responsible for the patient must attempt to identify the cause of each adverse event and its relationship to study drug treatment. Jones' algorithm is used for the causality assessment. The relationship with the study drug will be classified as follows:

### *CERTAIN*

There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

This means: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definite pharmacologically or phenomenologically\* using a using a satisfactory rechallenge procedure if necessary.

*\*i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon (for instance, 'grey baby syndrome' and chloramphenicol, or anaphylaxis immediately after the administration of a drug that had been given previously). This means that, if this criterion is not met, the relationship between the drug administration and the event onset can never be classified as 'Certain', even in the case of a positive rechallenge.*

### *PROBABLE*

There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

This means: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge).

Re-challenge information is not required for fulfilling this definition.

### *POSSIBLE*

There is some evidence to suggest a causal relationship; however, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).





This means: A clinical event, including laboratory test abnormality, with a reasonable time relationship to drug intake or application (topical forms), but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

*UNLIKELY*

There is another reasonable explanation for the event occurrence.

This means: A clinical event, including laboratory test abnormality, with a temporal relationship to drug intake that makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

*NOT ASSESSABLE*

There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

This means: A report of an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

*NOT RELATED*

There is no evidence of any causal relationship.

This means: When sufficient information exists to indicate that the etiology is unrelated to the study drug.

## **Severity classification**

Regardless of the classification of an adverse event as serious or non-serious, the severity of an adverse event will be rated according to the following definitions:

*MILD*

Symptom barely noticeable to study subject and that does not influence performance or functioning. Prescription drug not ordinarily needed for relief of symptom but may be given because of subject's personality.





*MODERATE*

Symptom of a sufficient severity to make the study subject uncomfortable with influence on the performance of daily activities. The subject is able to continue the study, even if treatment for symptoms may be needed.

*SEVERE*

Symptom causes severe discomfort. They may be of such severity that the study treatment has to be ended and the subject may be treated for symptoms and/or hospitalized.

It should be noted that a severe adverse event does not have to be serious in nature and vice versa. Contrary to the other two classifications (seriousness and causality), the classification of severity does not have any impact on reporting procedures.

**Exposure during pregnancy**

When the Investigator has received knowledge of exposure during pregnancy the pregnancy form should be fulfilled and forwarded to IBSA – DSU following the same timelines of SAE reporting. The pregnancy should be followed until delivery.





**Serious Adverse Event report (SAE)**

Please fax this report immediately at latest within 24 hours after first acknowledgment to [REDACTED]

<b>For IBSA internal use only</b>	<b>Case N°</b>	<b>Notice of</b>	<b>Day</b>	<b>Month</b>	<b>Year</b>
	<b>receipt</b>				
	.....				

<b>Type of report</b>	<b>Initial</b> <input type="checkbox"/>	<b>Follow Up</b> <input type="checkbox"/>	<b>nr. ....</b>
-----------------------	---	---	-----------------

<b>Study data</b>			
EUDRACT N°	IBSA Protocol N°	Site N°	Country where SAE occurred
.....	.....	.....	.....

<b>Patient data</b>					
Screening N°	Patient initials*	Date of birth	Sex	Weight (kg)	Pregnancy
.....	...../...../.....	...../...../.....	<input type="checkbox"/> male <input type="checkbox"/> female	.....	<input type="checkbox"/> Yes
Random N°	1st name / last name	day month year		Height (cm)	<input type="checkbox"/> No
.....	*if applicable according to law			.....	<input type="checkbox"/> Not applicable

<b>Seriousness criteria</b>	
Tick all boxes related to the SAE	<input type="checkbox"/> death <input type="checkbox"/> life threatening <input type="checkbox"/> inpatient hospitalization or prolongation of existing hospitalization <input type="checkbox"/> persistent or significant disability <input type="checkbox"/> congenital anomaly/birth defect <input type="checkbox"/> other medically important condition specify.....

**SAE(s) description**

<b>Diagnosis(es)</b>	<i>Please complete in order of importance</i>		
(if no diagnosis available give main symptoms)	<b>1</b>	<b>2</b>	<b>3</b>
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....
<b>Date and time of onset</b>	...../...../..... day month year ..... hours min	...../...../..... day month year ..... hours min	...../...../..... day month year ..... hours min
<b>Date and time ended</b>	...../...../..... day month year ..... hours min	...../...../..... day month year ..... hours min	...../...../..... day month year ..... hours min
<b>(tick continuing box if not ended)</b>	<input type="checkbox"/> continuing	<input type="checkbox"/> continuing	<input type="checkbox"/> continuing
<b>Severity / maximum intensity</b>	<input type="checkbox"/> 1. mild <input type="checkbox"/> 2. moderate <input type="checkbox"/> 3. severe	<input type="checkbox"/> 1. mild <input type="checkbox"/> 2. moderate <input type="checkbox"/> 3. severe	<input type="checkbox"/> 1. mild <input type="checkbox"/> 2. moderate <input type="checkbox"/> 3. severe
<b>Study drug relationship</b>	<input type="checkbox"/> 1. certain <input type="checkbox"/> 2. probable <input type="checkbox"/> 3. possible <input type="checkbox"/> 4. unlikely <input type="checkbox"/> 5. not assessable <input type="checkbox"/> 6. not related	<input type="checkbox"/> 1. certain <input type="checkbox"/> 2. probable <input type="checkbox"/> 3. possible <input type="checkbox"/> 4. unlikely <input type="checkbox"/> 5. not assessable <input type="checkbox"/> 6. not related	<input type="checkbox"/> 1. certain <input type="checkbox"/> 2. probable <input type="checkbox"/> 3. possible <input type="checkbox"/> 4. unlikely <input type="checkbox"/> 5. not assessable <input type="checkbox"/> 6. not related







**Serious Adverse Event report (SAE)**

EUDRACT N° .....	IBSA Protocol N° .....	Screening N° / Random N° ...../.....	Patient initials (if applicable) ...../..... (1st name / last name)
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**Additional information including course of SAE and comments**  
 Please, specify relevant information regarding diagnosis, causality assessment, relevant lab values etc.  
 .....  
 .....

**Investigational Medicinal Product (IMP)**

**Batch N°** .....

Indication for use: .....  
 IMP indication for use: .....

Code broken (If yes, please specify the date)  No  Yes ...../...../.....  Not applicable  
 day month year

IMP information	If open study or code broken, specify the name of IMP or brand name .....	Route of administration .....	Daily dosage .....
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IMP first administration: ...../...../..... hours min  
 day month year

IMP last administration before SAE: ...../...../..... hours min  
 day month year

SAE-related IMP action(s)	<input type="checkbox"/> 1. no action <input type="checkbox"/> 2. dose reduced <input type="checkbox"/> 3. dose increased <input type="checkbox"/> 4. temporary interrupted <input type="checkbox"/> 5. definitely interrupted	Comments (time periods, dosage changes, etc): ..... .....
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Similar previous experience  Yes  No Comments .....

Did the SAE abate after IMP discontinuation?  Yes  No  Not applicable

Did the SAE reappear after IMP re-administration?  Yes  No  Not applicable

**Concomitant medication(s) excluding SAE treatment**

Batch N°	Generic name (INN) (brand name for combination drug)	Indication for use	Daily dosage	Route of administration	First administration	Last administration
.....	.....	.....	.....	.....	...../...../..... day month year	ongoing <input type="checkbox"/> ...../...../..... day month year
.....	.....	.....	.....	.....	...../...../..... day month year	ongoing <input type="checkbox"/> ...../...../..... day month year
.....	.....	.....	.....	.....	...../...../..... day month year	ongoing <input type="checkbox"/> ...../...../..... day month year
.....	.....	.....	.....	.....	...../...../..... day month year	ongoing <input type="checkbox"/> ...../...../..... day month year





**Serious Adverse Event report (SAE)**

EUDRACT N° .....	IBSA Protocol N° .....	Screening N° / Random N° ...../.....	Patient initials (if applicable) ...../..... (1st name / last name)
<b>Specific SAE treatment (drugs, procedures)</b>			
Specific treatment of this SAE	none <input type="checkbox"/> drug treatment <input type="checkbox"/> no <input type="checkbox"/> yes (if yes, please, specify) ..... non-drug treatment <input type="checkbox"/> no <input type="checkbox"/> yes (if yes, please, specify) .....		
<b>Outcome (to date)</b>			
Tick the appropriate box relating to SAE	<input type="checkbox"/> 1. recovered / resolved <input type="checkbox"/> 2. recovered / resolved with sequelae (please, specify):..... ..... <input type="checkbox"/> 3. not recovered / not resolved → please provide further information as soon as possible <input type="checkbox"/> 4. recovering / resolving <input type="checkbox"/> 5. fatal → date of death: ...../...../..... day month year <input type="checkbox"/> 6. unknown (please, specify i.e. lost to follow up):..... .....		
In case of death	Cause of death: <input type="checkbox"/> progression of study disease <input type="checkbox"/> serious adverse event <input type="checkbox"/> other  Details of cause of death: ..... ..... ..... Autopsy done <input type="checkbox"/> Yes <input type="checkbox"/> No      Autopsy report available <input type="checkbox"/> Yes <input type="checkbox"/> No		
<b>Patient medical history</b>			
(Medical history, concomitant diseases, allergies, significant risk factors, laboratory findings, surgical procedures, biopsies, unusual circumstances, differential diagnosis, etc.) ..... ..... .....			
<b>Investigator details and/or stamp</b>			
Name ..... Address..... Tel. .... ..... Fax..... ..... Date: ...../...../.....      Investigator' signature: .....			





## **Appendix II**

### REPRESENTATIVE WRITTEN INFORMATION FOR PATIENT AND SAMPLE WRITTEN INFORMED CONSENT FORM

Provided separately.



### Appendix III

#### RESPONSIBILITIES OF THE CLINICAL INVESTIGATOR

*The Investigator is responsible for all trial related medical decisions.*

*The Investigator's responsibilities are as follows:*

- A. To take any trial related medical decision*
- B. to ensure that the clinical investigation is conducted according to the Protocol and applicable regulations;*
- C. to protect the rights, safety, and welfare of participants in the study;*
- D. to read the informative material provided by IBSA regarding the experimental drugs and supporting the rationale of the study;*
- E. to read this protocol and all its appendices thoroughly in order to fully comprehend the requirements of the study;*
- F. to be acquainted with the requirements of Good Clinical Practice and local legal requirements concerning clinical trials on human subjects (e.g. EU Directives, LA Ter/Oclin for Switzerland); should this not be the case, the Investigator is to ask for informative material and training that is to be given by the IBSA Clinical Monitor or other authorized Sponsor/CRO staff;*
- G. to ensure that appropriate facilities and adequate staff are available throughout the duration of the study;*
- H. to maintain a list of appropriately qualified persons to whom he/she has delegated significant trial related duties.*
- I. to ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational products and their trial related duties and functions.*
- J. to provide a copy of his/her updated curriculum vitae and medical credentials to the IBSA study Monitor and, if necessary, to the relevant Authorities;*
- K. to submit this protocol, Investigator Brochure (IB) and all the documents subject to review to the appropriate Ethics Review committee and any other*



*relevant Authority for approval prior to commencement of the study and during the trial, if not already submitted by IBSA;*

*L. to strictly adhere to the principles contained within the declaration of Helsinki; in particular the Investigator will not jeopardize the health or well-being of any subjects by unwarranted continuation of the study and will always obtain informed consent from every subject before including him/her in the study;*

*M. to administer drug only in accordance with the approved protocol and to participants under the investigator's personal supervision or under the supervision of a co-investigator; to not supply the investigational drug to any person not authorized;*

*N. to explain the correct use of the investigational products to each subject and check that each subject is following the instructions properly.*

*O. to maintain adequate records of the disposition of the drug, including dates, quantity, batch number, expiry date, code number and trial subject number and use by each participant. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for the disposition of the unused supplies of the drug (only under Sponsor's request).*

*P. to reconcile all investigational products received by IBSA.*

*Q. to store the investigational products as specified by IBSA.*

*R. to adhere to the protocol and make no amendment to the study protocol without prior discussion and written agreement with the Study Monitor and the Sponsor, except where necessary to eliminate an immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial (e.g. change in monitor, change of telephone numbers, etc.);*

*S. to document and explain any deviation from the approved protocol.*

*T. to collect, record and report data properly on the CRFs according to the instructions therein and to ensure that only authorized staff signs the pages of these documents;*

*U. to evaluate and to record all AEs and/or laboratory abnormalities occurring within the clinical study and evaluate their seriousness based on the protocol and provide medical care as indicated and documented appropriately; to notify the Study Monitor and the contact person of the Sponsor regarding adverse events as appropriate according to the rules laid down in the appendix pertaining to adverse events and the attached to this protocol;*





- V. to report immediately all Serious Adverse Events (SAEs) to IBSA, except those SAEs that protocol or other documents as IB identifies as not needing immediate reporting.*
- W. to ensure adequate medical care to subjects for any adverse events, including clinically significant laboratory values, or intercurrent illnesses occurring during the trial;*
- X. to accept monitoring and also auditing of the study by IBSA authorized staff, or CRO staff authorized by IBSA and/or regulatory authorities; in particular the Investigator agrees to grant adequate access to facilities and archives and will ensure that his staff will dedicate sufficient time to these activities;*
- Y. to store subject identification codes and source raw data for the maximum period foreseen by the hospital and local legislation (essential documents should be stored for at least 10 years after study completion). Should the hospital archive not be organized to store data for this period of time, the Study Monitor is to be informed so that adequate provision can be made for archiving together with IBSA;*
- Z. to make reasonable efforts to ascertain the reasons for subject's premature withdrawal from the study, fully respecting subject's right and considering that subject is not obliged to explain them.*
- AA. to treat any unpublished information supplied by IBSA as confidential and ensure that confidentiality is kept also by all staff involved in this project. In this respect, no data will be used for presentations at scientific meetings and/or publication in scientific journals without prior agreement with IBSA.*

