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Bioequivalence of two formulations of Levothyroxine sodium 200mcg under tablet form.

PPD

A prospective, single dose, randomized, open-label, crossover, comparative study to establish bioequivalence in healthy subjects between the Puran T4® (Sanofi Aventis Farmacêutica Ltda) vs. the new formulation of levothyroxine (Eutirox NF® Merck) administered orally as 3 tablets of 200 µg.

PPD / ***Researchers***
PPD
PPD / ***Principal Investigator*****:** PPD .
Clinical Investigator**:** PPD .

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PPD .

PPD /Version Control

PPD /Version	PPD /Date	PPD / Reason of version
1.0	PPD 018	PPD / *Not applicable.*
2.0	PPD 29/September/2018	PPD / Not applicable
3.0	PPD 2018	PPD / Not applicable
4.0	PPD 018	PPD / Changes as requested by the

PPD / Synopsis

PPD / Study Title	PPD *A prospective, single dose, randomized, open-label, crossover, comparative study to establish bioequivalence in healthy subjects between the Puran T4® (Sanofi Aventis Farmacêutica Ltda) vs. the new formulation of levothyroxine (Eutirox NF® Merck) administered ts of 200 µg.*
PPD / PPD Protocol number	PPD
PPD Merck Protocol number	014
PPD / Active Principal Code	LVT
PPD / Study Medication	PPD *Test: Eutirox NF® - Levothyroxine sodium 200mcg tablet; Merck, S.A. de C.V.* *Comparator: Puran T4® - Levothyroxine sodium 200mcg tablet; Sanofi-Aventis Farmacêutica Ltda.*
PPD / Study's Objective	PPD *The study objective is to verify through a single dose study, if the test formulation of Levothyroxine sodium presents an equivalent rate and extension of absorption to the comparator formulation when administered with the same dosage and under fasting conditions and after baseline correction concentrations.*
PPD / Number of	PPD *72 healthy research participants (36 males and 36 females).* *The participants will be divided into two admission subgroups, as*

	described in "confinement form of research participants" protocol.
PPD / ***Study Design***	PPD *Open, randomized, two treatments (A and B), two sequences (AB and BA), two subgroups, truncated, two periods, crossover and single dose.*
PPD / ***Washout***	PPD *The treatments will be investigated in this study with an interval between the periods of at least 65 days.*
PPD / ***Dose***	PPD *600mcg of Levothyroxine Sodium equivalent to 3 tablets of the test drug **or** 3 tablets of the comparator drug.*
PPD / ***Collection Time***	PPD *In each study period will be collected blood in the following times: : (-) 00:30 (baseline); (-) 00:15 (baseline); 00:00 (5 minutes before dosing);* 0:30; 01:00; 01:30; 02:00; 02:30; 03:00; 03:15; 03:30; 03:45; 04:00; 04:15; 04:30; 04:45; 05:00; 05:30; 06:00; 06:30; 08:00; 10:00; 12:00; 24:00; 36:00; 48:00 and 72 *hours after the administration of the medication.*
PPD / ***Confinement period***	PPD *24 hours.*
PPD / ***Safety procedures***	PPD *Monitoring clinical tolerability (adverse events, laboratory parameters), pregnancy test (urinary) for women before each study period, vital signs (blood pressure, temperature and heart rate), ECG, total and free T3 and T4, and TSH.*

PPD / Post study procedures	PPD *Laboratory examinations (hematological, biochemical, urinalysis) adverse events monitoring and ECG.* *B-HCG for women after the last blood collection of the last period.*
PPD / Analytical Methodology	PPD *Determination of Levothyroxine (T4) by techniques of liquid chromatography coupled to tandem mass spectrometry (LC MS/MS).*
PPD / Pharmacokinetic	PPD *Primary: $C_{max,adj}$; $AUC_{0-72,adj}$* *Secondary: Tmax., AUC_{0-72} and C_{max}.*
PPD Baseline adjusted	PPD *Difference between each point of the plasma concentration curve of each research participant/period and the mean of the basal levels (3 points). Negative values will be automatically replaced with zero.*
PPD /Statistical Analysis	PPD *The calculated 90% confidence interval of the ratio of plasma levothyroxine (T4) concentration, calculated from the geometric means of the Ln transformed values, should fall between 80% - 125% for $C_{max,adj}$ and $AUC_{0-72,adj}$.*
PPD / Adverse events	PPD *The observed or mentioned (via nonspecific questions) adverse events will be documented, analysed and reported according to their severity and causality.*

PPD / Data analysis plan	PPD *Descriptive statistics, relative bioavailability estimation, construction of confidence intervals (parametric and non-parametric), application of an ANOVA.*

Responsáveis pelas etapas do estudo / *Responsibilities for the phases of study*

PPD /	Merck, S.A.
PPD	PPD
PPD /	PPD

PPD / *Phase -Institution*	PPD /	PPD /
PPD / **Clinical Phase -** PPD	PPD	PPD / *Pharmacist Biochemisty*
PPD **Laboratorial Exams execution -** PPD PPD		PPD / *Pharmacist Biochemisty*
PPD / ***Analytical Phase***		PPD / *Chemisty*
PPD / **Statistical Phase -** PPD		PPD
PPD / **Quality Assurance -** PPD		PPD / Biologist

PPD / ***Study researchers signature***

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This project will be conducted according to the norms and rules of research with human beings as in Resolution Nº 466/12 and 251/97 of the National Health Committee – Health Ministry, of GCP – Good Clinical Practices according ICH and the Helsinki Declaration (1964) also the Tokyo's review (1975), Venice's review (1983), Hong Kong's review (1989), Somerset West's review (1996), Edinburg's review (2000), Washington's review (2002), Tokyo's review (2004), Seoul's review (2008) and Fortaleza's review (2013). The Principles of Good Laboratory Practice – GLP (NIT-Dicla-035) will also be obeyed.

PPD / ***Study Sponsor***

Merck, S.A._____Data/ *Date*___/___/___.

PPD / PPD ***team***

PPD / ***Principal investigator***

PPD._____ Data/*Date*___/___/___.

PPD

PPD / ***Clinical investigator***

PPD _____Data/*Date*___/___/___.

(Médico/*Physician* – PPD)

PPD / ***Institutions involved in the study***

PPD / ***Study Sponsor:***
PPD / *Study Sponsor's name*: Merck, S.A.
PPD / *Address*: Estrada dos Bandeirantes 1099 – Jacarepaguá, Rio de Janeiro, RJ – Brasil.

PPD /
Place where the research participant clinical evaluation and the Clinical and Statistical Phase will take place:
PPD / ***Clinical and statistical Unit***
PPD
PPD

PPD / ***Place of the laboratory and clinical exams:***
PPD .:
PPD
PPD

PPD / ***Place where the Analytical Phases will take place:***
PPD / ***Analytical Unit***
PPD
PPD
.

PPD / ***Ethics Committee responsible for evaluating and approving the protocol:***
PPD
PPD
.

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Glossary, acronyms and abbreviations

Acronyms/Abbreviations	*Meaning*
ANOVA	*Variance analysis*
ANVISA	*National Agency of Sanitary Surveillance*
AUC_{0-72}	*Area under the curve, from time zero to 72 hours*
$AUC_{0-72,adj}$	*Area under the curve, from time zero to 72 hours, ajusted by mean basal concentration*
REC	*Research Ethics Committee*
HPLC	*High performance liquid chromatography*
C_{max}	*Maximum reached plasma concentration*
$C_{max,adj}$	*Maximum reached plasma concentration, ajusted by mean basal concentration*
NHC/HM	*National Health Committee – Health Ministry*
NECR	*National Ethics Committee and Research*
QC	*Quality control*
HCQA	*High concentration quality assurance*
LCQA	*Low concentration quality assurance*
QLQA	*Quantification limit quality assurance*
MCQA	*Medium concentration quality assurance*
Ct	*Last drug concentration experimentally determined*
CV	*Coefficient of Variation*
D	*Depuration*
FLR	*Fluorescence*
CI	*Confidence interval*
PPD	
QL	*Quantification limit*
lz	*Terminal phase elimination constant*
MS	*Spectrophotometry*
m/z	*Mass/ load ratio*
SPE	*Solid phase extraction*
GOT	*Glutemic oxaloacetic transaminase*
GTP	*Glutemic pyruvic transaminase*
T_{max}	*Necessary time to reach the Cmax*
TXA_2	*Thromboxane A2*
UV	*Ultraviolet*
Vd	*Distribution volume*

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Chronogram of the study

Procedure	*Pre-study procedures*	*Period 1 and 2*	*Post-study procedures*
Explanatory lecture[1]	*X*		
Recruitment and Participants Screening Form	*X*		
Informed consent form for Genotyping Exam	*X*		
Informed consent form	*X*		
Clinical evaluation[2]	*X*	*X*	*X*
Blood pressure, pulse, temperature	*X*	*X*	*X*
Electrocardiogram	*-7 days to 0 day prior to period 1*		*X*
Laboratorial Exams[3]	*- 3 months before Period 1*		*X*
Meeting pre-confinement	*- 15 days before Period 1*		
Pregnancy test, from plasma[4]	*X*		*X*
Pregnancy test, from urine[4]		*X*	
Testing for alcohol and drugs[5]		*X*	
Confinement		*from at least 12 hours prior to drug administration until 12 hours following drug administration*	
Fasting	*minimum of 12 hours of fasting before the perform laboratorial exam*	*from at least 8 hours prior to drug administration until 4 hours following drug administration*	*minimum of 12 hours of fasting before the laboratorial exams*
Standardized meals and drinks		*X*	
Administration of the drug in study		*X*	
Blood collection for pharmacokinetic analysis		*X*	
Safety procedures (monitoring for adverse events)	→	→	→
Check on concomitant medication	→	→	→
Control under restrictions and prohibitions[6]	*X*	*X*	
Discharge from study[7]			*X*

Note: The schedule for the research will be carried out only if the project is APPROVED by CEP / CONEP system

1 – The explanatory lecture will only be given to those who have never participated in any studies in PPD

2 – The pre-study clinical evaluation is done after the signing of the Recruitment and Research Participants Screening Form. The clinical evaluation during pre-confinement is done at the day of admission at each period and the clinical evaluation before discharge is performed on the day the participant is released from the confinement.

3 – The laboratorial exams pre-study are complete blood count (erythrogram and leukogram); blood biochemistry (free T3 and T4, TSH, blood glucose, total proteins, albumin, transaminases, alkaline phosphatase, creatinine, urea, uric acid, total, conjugated and unconjugated bilirubins, total cholesterol, triglycerides), urinalysis (urin I), b-HCG for women, serological tests (Hepatitis B, Hepatitis C, HIV 1 and 2). The laboratorial exams post-study are blood count (erythrogram and leukogram); blood biochemistry (blood glucose, total proteins, albumin, transaminases, alkaline phosphatase, creatinine, urea, uric acid, total, conjugated and unconjugated bilirubins, total cholesterol, triglycerides), urinalysis (urin I), b-HCG for women and total and free T3, total and free T4, TSH

4 – In the pre and post-study periods, a ß-hCG pregnancy test will be performed from plasma and a urinary pregnancy test will also be performed at the day of admission during each period.

5 – The test for alcohol use and drug abuse will be held on the day of admission during each period.

6 – All the restrictions and prohibitions that should be checked before and during the study, will be described in "Restrictions and prohibitions: before, during and after the study".

7 – In the case of a withdrawal, exit procedures should be done as soon as possible.

PPD / Tables

PPD / Figures

Índice

1 - Introdução

1.1 PPD / *Background information*

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Congenital hypothyroidism (CH) is the most frequent cause of preventable mental retardation. More than 90% CH cases are primary origin and treatment is to replace the thyroid hormone deficiency with dosage adjustment according to age and clinical and biochemical conditions of the patient (Rojas et al. 2009).

At present, an optimal therapy for hypothyroidism requires the replacement of the deficiency of thyroid hormone with synthetic levothyroxine. The drug is also used as an interventional therapy to suppress thyroid stimulating hormone (TSH) secretion in patients with nodular thyroid disease or thyroid cancer. As the incidence of overt hypothyroidism occurs in 1.5% to 2% of women and 0.2% in men, and its incidence increases with age to 6% and 2.5% in women and men aged over 60 years, respectively, levothyroxine is one of the most commonly prescribed medications in the United States (Koytchev R. & Lauschner R., 2004).

In Brazil, the current bioequivalence standards to establish bioequivalence of drug products typically use the accepted 2 treatment - 2 period - 2 sequence crossover design and compare blood levels of drug between test and reference products over time after a single

dose, administered to healthy volunteers. From these data, the maximum observed blood concentration ($C_{max,adj}$) and the area under the curve vs time (AUC_{adj}) truncated for 72 hours are calculated for each product, using a logarithmic transformation and then this results are compared (RE1170), both pharmacokinetic metrics going to be determined by the baseline value obtained from the average of three levothyroxine measurements taken before dosing (0.5, 0.25 and 0 h pre-dose).

If the comparison of the calculated mean C_{max} and AUC baseline-corrected parameters meets the acceptance criteria, then the test product is deemed bioequivalent to the reference product. Because of variability owing to subject differences and possible small differences between the products, ANVISA's resolution RE1170 has recommended that 90% confidence intervals be placed on the ratio of test to reference for $AUC_{0-72,adj}$ and $C_{max,adj}$, and this interval be within 80% to 125% (based on the antilog of the log ratio) to demonstrate bioequivalence.

1.2 PPD / *Drug description*

1.2.1 PPD / *Active Principle´s name*

PPD / *Levothyroxine Sodium.*

1.2.2 PPD / *Molecular Formula*

$C_{15}H_{11}I_4NNaO_4$ (eMolecules, 2017)

1.2.3 PPD / *Molar mass*

798,85 (eMolecules, 2017)

1.2.4 PPD / *Description*

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Levothyroxine is white to yellowish-white, odorless, hygroscopic. When in contact with light it may take on the pink coloration. It should be stored protected from light and in airtight containers (MARTINDALE, 2002).

1.2.5 PPD / *Solubility*

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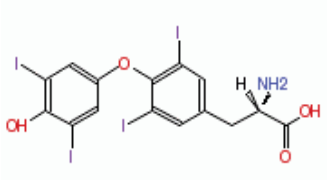
Levothyroxine is soluble in water and alcohol and insoluble in acetone, chloroform and ether (MARTINDALE, 2002).

1.2.6 PPD / Chemical Structure



PPD / *Figure 1 – Chemical Structure of Levothyroxine Sodium*
(Site emol uery=Levothyroxine%20sodium&system-type=BB&p=1).

1.3 PPD / *Levothyroxine sodium*

PPD

Thyroid hormones exert both catabolic (calorigenic) and anabolic effects. Therefore, they are comprised in the metabolism, growth and development, especially the central nervous system of infants. The two most important hormones are triiodothyronine (T3) and thyroxine (T4) (KOROKOLVAS, 2006; SILVA, 2006). The levothyroxine amounts released into the circulation by a functioning thyroid gland are regulated by the amount of thyrotropin (TSH) secreted by the anterior part of the pituitary gland. TSH synthesis is regulated by circulating levothyroxine and triiodothyronine levels (negative feedback) and thyrotropin-releasing hormone (TRH) secreted by the hypothalamus (SILVA, 2006).

The levothyroxine is the main hormone produced by the thyroid and its function is to stimulate the cellular metabolism (Cerutti, R. et al, 1999).

Levothyroxine sodium is obtained by synthesis and corresponds to the sodium salt of the levorotatory isomer of thyroxine. Levothyroxine is a biochemical and physiologically identical compound to the endogenous T4 hormone and is usually the drug of choice in hypothyroidism replacement therapy (BLAKESLEY et al., 2004). The drug is also used in thyroid stimulating hormone suppression therapy and in patients with thyroid nodule or cancer (KYYCHEV and LAUSCHNER, 2004). Doses in the treatment of hypothyroidism are individualized, based on clinical response and thyroid function assay results; vary according to the size and age of the patient (KOROKOLVAS, 2006).

1.3.1 PPD / *Pharmacokinetic*

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Absorption: administered orally, levothyroxine absorption is incomplete and variable, around 50% to 80%, especially when administered with food. The ileum and colon are the sites where most of absorption takes place (MARTINDALE, 2002; KOYTCHEV, 2004; KOROKOLVAS, 2006; SILVA, 2006). This variation in absorption is dependent on several factors, such as: vehicles, intestinal flora, dietary, foods, concomitant medications (SILVA, 2006).

Following oral administration, the maximum plasma level of levothyroxine is reached from 2 to 4 hours. The ingestion of levothyroxine in fasting conditions increases its absorption (MARTINDALE, 2002).

Distribution: linked to plasma proteins (TGB, albumin and transthyretin) thyroxine is distributed in a volume of 10L (MARTINDALE, 2002; SILVA, 2006). Thyroid hormones cross the placenta and can be found in breast milk (MARTINDALE, 2002).

Metabolism: the metabolism of thyroxine occurs by deiodination and has as its product triiodothyronine (35%) (SILVA, 2006). Levothyroxine has a plasma half-life of 6 to 7 days (KOYTCHEV, 2004). According to Martindale (2002) levothyroxine is primarily

metabolized in the liver and kidneys in T3 and about 40% is biotransformed in reverse (inactive) T3 and both undergo deiodination to form inactive metabolites.

Excretion: the untransformed T4 portion of T3 is eliminated by feces after conjugation with glucuronides and sulfate (SILVA, 2006). According to Martindale (2002) levothyroxine undergoes recirculation.

According to the Summary of Products Characteristics (2015, orally given levothyroxine is absorbed almost exclusively in the upper small intestine. Depending on the galenical formulation absorption amounts up to 80% and Ttmax is approximately 5 to 6 hours.

Following oral administration the onset of action is seen after 3-5 days. Levothyroxine exhibits an extremely high binding to specific transport proteins of about 99.97 %. This protein hormone binding is not covalent and so the bound hormone in plasma is in continuous and very rapid exchange with the fraction of the free hormone.

Due to its high protein binding levothyroxine undergoes neither haemodialysis nor haemoperfusion. The half-life of levothyroxine is on average 7 days. In hyperthyroidism it is shorter (3-4 days) and in hypothyroidism it is longer (approx. 9-10 days). The volume of distribution amounts to about 10-12 l. The liver contains 1/3 of the entire extra-thyroidal levothyroxine, which is rapidly exchangeable with the levothyroxine in serum. Thyroid hormones are metabolized mainly in the liver, kidneys, brain and muscles. The metabolites are excreted with urine and faeces. The overall metabolic clearance for levothyroxine is about 1.2 l plasma/day.

1.3.2 PPD / *Indications*

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Levothyroxine is a thyroid hormone used in hormone replacement therapy and in the treatment of hypothyroidism. Levothyroxine should be used in cases of nontoxic diffuse goiter, Hashimoto's thyroiditis so that TSH secretion is suppressed and thereby prevent or reverse an enlargement of the thyroid. TSH suppression through the use of levothyroxine can be used in the treatment of thyroid carcinoma and as a differential diagnosis for hyperthyroidism (MARTINDALE, 2002).

In the treatment of hypothyroidism in adults, the initial dose is 50 to 100 mcg of levothyroxine sodium per day orally and may be increased from 25 to 50 mcg at intervals of 4 weeks until it has been obtained and therapeutic effect and the dose stabilized (MARTINDALE, 2002).

1.3.3 PPD

Warnings and Precautions (Puran T4®, leaflet reference drug)

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WARNINGS

- *Levothyroxine should be used with extreme caution in patients with cardiovascular disorders, including angina pectoris, heart failure, myocardial infarction, and hypertension; if necessary, lower starting doses, small dose increases, and longer intervals between dose increases should be used.*
- *Special care should be taken in elderly patients with goiter and normal thyroid function, who have already had myocardial infarction or who have angina pectoris, heart failure or arrhythmia with tachycardia.*
- *Thyroid replacement therapy may precipitate an acute adrenal crisis in patients with adrenal insufficiency or pituitary insufficiency without adequate corticosteroid.*
- *In preterm infants with low weight, initiation of levothyroxine therapy should be exercised with extreme caution, as circulatory collapse may occur due to immature adrenal function.*
- *Caution is advised when levothyroxine is administered in patients with a known history of epilepsy, because in these patients there is an increased risk of seizures.*

Effects on bone mineral density: the use of levothyroxine may be associated with risk of bone loss, with consequent development of osteoporosis and fractures. This risk was observed in some studies in postmenopausal women using suppressive doses of TSH after differentiated thyroid carcinoma.

PRECAUTIONS

Levothyroxine should be introduced very gradually in elderly patients and in those with long-standing hypothyroidism in order to avoid any sudden increase in metabolic needs.

Thyroid hormones should not be used for weight reduction. In euthyroid patients, normal dosages are not effective for weight loss; higher dosages may produce severe or even threatening manifestations, especially if given with other specific weight reduction treatments.
Additional care is required when levothyroxine is administered to patients with diabetes mellitus or diabetes insipidus.
The dosage should be adjusted according to thyroid function tests (TSH +/- L-T4). Patient monitoring should be performed according to clinical symptoms as well as thyroid function tests.

1.3.4 PPD /*Drug interactions*

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Drug interactions with levothyroxine are:
Antiarrhythmics: Amiodarone can inhibit the conversion (iodination) of thyroxine to triiodothyroxine, which results in a decrease in triiodothyroxine concentration and a consequent increase in reverse triiodothyroxine (MARTINDALE, 2002).
Antibacterials: rifampicin-induced enzymes increase the metabolism of thyroid hormones resulting in a reduced concentration of them (MARTINDALE, 2002).
Anticoagulants: Thyroid hormones increase the effects of oral anticoagulants (MARTINDALE, 2002).
Antidepressants: Some drugs, such as lithium, act directly on the thyroid and inhibit the release of thyroid hormones (MARTINDALE, 2002).
Antidiabetics: The use of medication can affect the state of the disease and its treatment. In hypothyroid diabetics, the use of levothyroxine may increase the need for insulin or oral hypoglycemic agents (MARTINDALE, 2002).

Antiretrovirals: Combination of levothyroxine with antiviral, such as ritonavir, may lead to increased use of levothyroxine (MARTINDALE, 2002).
Antiepileptics: Some drugs such as carbamazepine, phenytoin or barbiturates may increase the metabolism of thyroid hormones (MARTINDALE, 2002).
Gastrointestinal drugs: Sucralfate reduces the absorption of levothyroxine by the gastrointestinal tract, as well as aluminum hydroxide and calcium carbonate (MARTINDALE, 2002).
Estrogenic derivatives: estrogenic derivatives may decrease the therapeutic effect of thyroid products (MARTINDALE, 2002).
Acetylsalicylic acid can alter thyroid function parameters by competing with thyroid hormones in binding to the carrier proteins (TBG mainly) (MARTINDALE, 2002).

1.3.5 PPD /

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Very common reaction (≥ 1/10)

Common reaction (≥ 1/100 and < 1/10)

Unusual reaction (≥ 1/1.000 and < 1/100)

Rare reaction (≥ 1/10.000 and < 1/1.000)

Very rare reaction (< 1/10.000)

Unknown reaction (cannot be estimated from the available data)

In general, the adverse reactions of levothyroxine are associated with an excessive dosage and correspond to the symptoms of hyperthyroidism.

- *Heart disorders*

Very common: palpitations.

Common: tachycardia.

Unknown: cardiac arrhythmias and angina pain.

- *Skin and subcutaneous disorders*

Unknown: rash, hives and sweating.

- *Psychiatric disorders*

Very common: insomnia.

Common: nervousness.

Unknown: excitability.

- *Musculoskeletal and connective tissue disorders*

Unknown: muscle weakness and cramps, osteoporosis in suppressive doses of levothyroxine, especially in postmenopausal women, especially when treated for a long period.

- *Vascular disorders*

Unknown: hot flashes, circulatory collapse in preterm low birth weight infants.

- *Disorders of the reproductive system and breast*

Unknown: menstrual irregularities.

- *Gastrointestinal disorders*

Unknown: diarrhea and vomiting.

- *Investigations*

Unknown: weight loss.

- *Nervous system disorders*

Very common: headache.

Unknown: tremors, benign intracranial hypertension particularly in children.

- *General disorders and administration site conditions*

Unknown: heat intolerance, fever.

- *Endocrine disorders*

Common: hyperthyroidism.

Such effects generally disappear with reduced dosage or temporary withdrawal of treatment.

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Relative Bioavailability/Bioequivalence Study

Protocol - according to RE # 894, dated 5/29/2003.

PPD

2 - Project title

Pharmaceutical bioequivalence evaluation of the pharmaco Levothyroxine sodium – Eutirox® 200mcg (Merck, S.A. de C.V.) under tablet form versus Puran T4® 200mcg (Sanofi-Aventis Farmacêutica Ltda.) under tablet form, in healthy male and female research participants under fasting conditions, using techniques Liquid Chromatography.

PPD

Merck, S.A.

3 Study sponsor

Merck, S.A.

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4 Study objective

The study objective is to verify through a single dose study, if the test formulation of Levothyroxine sodium presents an equivalent rate and extension of absorption to the comparator formulation when administered with the same dosage and under fasting conditions and after baseline correction concentrations.

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5 Study design

Every study is designed in order to allow that primary pharmacokinetic parameters estimations ($C_{max,\ adj}$, $AUC_{0\text{-}72,\ adj}$) are obtained free from the interference of any foreign factor that might negatively influence the comparison between the formulations. This way, the search for the

standardization of the research subjects conditions will be attempted once only through this standardization there will be confidence enough to reach the final conclusion if both drugs are bioequivalent or not when given in the same conditions.

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5.1 Type

Single center, open-label, cross, randomized, prospective, two treatments (A and B), two periods, 2 subgroups, two sequences (AB and BA), truncated, using 72 healthy research participants*, with ages raging between 18 and 50 years old. The participant will receive, at each period, the test formulation or the comparator formulation according to the randomization list (Annex 6) under fasting conditions.*
*According to the resolution RE # 1170, dated April 19, 2006, the interval between periods (washout) must be of, at least, seven elimination half-lives of the drug and/or metabolite. The drug mentioned, Levothyroxine sodium, have a half-life of approximately 6 to 7 days, therefore, the washout period of the study should be at least 65 days to guarantee that the drug has been completely eliminated from the body, but a*ccording PPD experience, the washout will be 65 because in a previous trials in the PPD showed a significant effect of levothyroxine (T4) in the 2 period independently of the randomization method (probably du o the TSH suppression and consequently decrease of endogenous levels of levothyroxine).
According to the resolution RE # 1170, dated April 19, 2006, letter "q", in the case of drugs that show half-life long (more than 24 hours) can be used an alternative collection chronogram, a minimum of 72 hours which allows the determination of the truncated area under the curve ($AUC_{0-72, adj}$).
In this study, for the drug will be conducting Levothyroxine sodium truncation in 72 hours considering the value of the half-life of approximately 6 to 7 days.

6 PPD / *Study population*

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6.1 Detailed description

At least 72 research participants (36 male and 36 female) of ages between 18 and 50 years old. The BMI - Body Mass Index of the participants must be comprised within the range of 18,50 to 24,90, for this study will be accepted a range of 18,50 to 27,00.). There are no restrictions regarding the ethnic group.

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6.2 Research Participant screening

The research participants will be recruited among those who visit the PPD *Clinical Site. Before being submitted to any evaluation, the participants will have all the questions answered, and if they agree, they will sign the recruitment and research participants screening form which was approved by the Ethics Committee in Research of the Institute of Pharmaceutical Sciences -* PPD *accredited by the National Commission for Ethics in Research (CONEP) CNS/MS.*

6.3 Triagem

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6.3.1 Clinical evaluation

According to SOP CLIN 006 (Research Participant Recruitment and Selection) PPD *clinical evaluation will be divided in phase 1 and phase 2. The physician and/or nurse should first realize phase 1 of the clinical evaluation and if the participant is considered apt will go through phase 2 of the clinical evaluation. If the participant is considered unapt in the phase 1 will not go to phase 2: it may be dismissed immediately by the physician and/or nurse or go through treatment.*

When the Research Participant goes to treatment may be allocated for months and come back for accompanying many times. It will be realized phase 2 of the clinical evaluation only when the participant becomes apt.

After phase 2 of the clinical evaluation by a physician, the Research Participant will have 3 months to realize the first laboratorial exams. It is necessary to highlight, that in each time the participant visits PPD *for accompanying of the treatment the clinical evaluation for phase 1 will be revised and actualized.*

In the clinical evaluation, the candidates to Research Participant should not present signs or evident symptoms of any cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal or hematological disease. To verify it will be realized an anamnesis, as well as the evaluation of the biochemical and hematological laboratorial exams as related in item 6.3.2.

During the clinical evaluation, the Research Participant will be classified according to the racial group they belong. To this race classification will be used the auto declaration method, in which the subject will auto declare as part of a racial group according to the following definitions: white, black, mulatto, yellow or Indian. The physician and/or nurse has to register the declared racial group in the clinical evaluation form.

The Research Participant will only be accepted in the study if they are considered healthy as determined by the clinical evaluation and in the laboratory exams done before the beginning of the study and if the satisfy the criteria established in items 6.4 and 6.5. The laboratorial exams done in the pre study period will be valid for 3 months and the electrocardiogram will be performed 7 days prior to period 1 of confinement.

After proved the state of health, they will be submitted to an interview with the doctor to evaluate their mental health, as well as the emotional state to participate in the investigation.

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6.3.2 Clinical and lab tests

The Research Participants will be submitted to the following clinical and lab tests:

- *Electrocardiogram (12-leads);*
- *Testing for alcohol at the time the Research Participant arrives to the hospital during periods 1 and 2;*
- *Testing for drugs of abuse at the arrival of the Research Participant to the hospital in periods 1 and 2;*
- *Pregnancy test on arrival for Research Participant hospitalization during periods 1 and 2;*
- *Blood tests: complete blood count (erythrogram and leukogram);*
- *Chemical tests: urea, creatinine, bilirubin (total and fractions), total proteins, albumin, blood glucose, alkaline phosphatase, SGOT, SGPT, total cholesterol, triglycerides and uric acid;*
- *Tests: free and total T3 and T4, TSH;*
- *Serological tests: hepatitis B (HBsAg and IgM Anti HBc), hepatitis C, HIV 1 and 2;*
- *Urinalysis;*
- *Serum βHCG test for women.*

Obs: Hepatitis B, hepatitis C, and HIV 1 and 2 tests will be performed only during the pre-study period. Test Pregnancy for women will be repeated at the moment of hospitalization (Period 1 and 2) by urine dipstick.

Drugs likely to be detected in drug testing are: Methamphetamine, Opiate, Morphine, Tetrahydrocannabinol – THC (Marijuana), Amphetamine, Benzoylecgonine (Cocaine) and Benzodiazepine.

PPD *will provide a copy of the pre-study and post-study lab tests to the research participant.*

The clinical and lab tests files, the CRFs, dossiers, and charts will be stored by the PPD *for at least 10 years, according to Resolution – RDC # 56 dated 8/oct/2014. Whenever needed, due to some complication,* PPD *will provide a copy of the papers to the research participant.*

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6.4 Inclusion criteria

The following criteria must be satisfactory to the research participants can be included in the study:

1. *To have freely agreed and signed the consent form, after all essential elements of the protocol have been clarified, before any procedure.*
2. *Healthy males and non-pregnant females volunteers.*
3. *Between 18 and 50 years old.*
4. *BMI - Body Mass Index of the research participants must be comprised within the range of 18.50 to 27.00.*

5 *No abnormal findings on medical history that, in the opinion of the investigator, constitutes a risk or a contraindication for the participation of the subject in the study or that could interfere with the study objectives, conduct or evaluation.*
6 *Normal vital signs: heart rate between 50 and 100 beats per minute; Systolic pressure between 80 and 129 mmHg; diastolic pressure between 50 and 89 mmHg; temperature between 36.0 and 37.0 ° C.*
7 *Electrocardiogram [ECG] normal (Abnormalities, even if clinically not relevant, are not permitted (e.g. PR, QRS, QT, QTcF should be within normal range, no conduction abnormalities etc).*
8 *All values for biochemistry and hematology tests of blood and urine within the normal range or showing no clinically relevant deviation as judged by the Investigator.*
9 *Subjects with thyroid profile results within normal ranges (total and free T3 and T4, and TSH must be within normal ranges).*
10 *Biosafety tests negative for the presence of human immunodeficiency virus [HIV], hepatitis B [HBV] and Hepatitis C [HCV].*
11 *Subjects with negative results in screening tests for drugs of abuse such as amphetamines, benzodiazepines, cocaine, methamphetamines, morphine and tetrahydrocannabinoids.*
12 *Subjects with negative alcohol test.*
13 *Women with negative (qualitative and quantitative) pregnancy tests at screening and at admission in each period.*
14 *Subjects must not have a history of alcohol abuse (an average daily intake of more than 3 units or a weekly intake of more than 21 units where 1 unit equals 340 mL of beer, 115 mL of wine or 43 mL of spirits), psychoactive substances or chronic use of drugs.*
15 *Nonsmoker for at least 3 months.*
16 *All women of childbearing potential who are not pregnant or breastfeeding and who are using a highly effective contraceptive method (defined as those, alone or combined, which failure rate is low; i.e., less than 1 % a year, when used continuously and correctly) for at least one month before first and following last dosing. Barrier methods and intrauterine device are considered standard contraceptive methods. Hormonal methods will not be included. Post-menopausal women can be included (i.e., those with at least 12 consecutive months of amenorrhea following their last menstruation period) or surgically sterile/hysterectomy for at least 6 months before their participation in the study.*

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6.5 Exclusion criteria

Any of the following criteria below will exclude the study research participant:

1- *Supplementary tests results out of the values considered as normal, unless considered clinically irrelevant;*
2- *Research participants who are submitted to surgery before the beginning of the study will be carefully evaluated by the doctor regarding the enrollment in the study complying to an exclusion period ranging from 4 to 8 weeks;*
3- *Positive test for hepatitis B, hepatitis C, or HIV in pre-study tests;*
4- *Subjects with a history of hypersensitivity/allergy to study drug or excipients, history or presence of asthma or any serious allergy (requiring hospitalization or prolonged systemic treatment), any food allergy or intolerance which in the opinion of the Investigator represents a safety risk (e.g. iodine allergy, etc.)*
5- *Has participated in any experimental trial or has taken any experimental drug within 6 months previous to this study (RDC Resolution # 34, dated June 3, 2008);*
6- *Subjects that prior to the dosing takes any other medication and had not passed at least seven half-lives of elimination of the drug, in this case, be considered by the Principal Investigator the non-inclusion of the subject in the study. Subjects taking medications known to affect thyroid hormone metabolism, e.g., oral contraceptives, hormonal implants, parenteral hormones, anabolic steroids, androgens, etc., or the bioavailability of levothyroxine like proton pump Inhibitors.*
7- *Has a history of alcohol abuse or has ingested alcohol 24 hours previous to the hospitalization period;*
8- *Has a history of drug abuse [patients using marijuana and hashish less than 3 months before the visit will be excluded. For drugs such as cocaine, phencyclidine (PCP), crack, heroin less than 1 year before the visit are excluded];*
9- *Subjects who have been exposed to agents known as inducers or inhibitors of hepatic enzyme systems or have potentially toxic medications taken within thirty days before the start of the study.*
10- *Use of monoamine oxidase (MAO) inhibitors (moclobemide, iproniazid, nialamide, phenelzine, tranylcypromine) two weeks before the beginning of treatment;*
11- *Use of serotonin reuptake inhibitors (duloxetin, milnacipran, nefazodone, venlafaxin, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, fluvoxamine);*
12- *To present any psychiatric and/or psychological disease (including depression), unless considered clinically not significant by the clinical investigator;*
13- *Has a clinically significant history and/or presence of gastrointestinal disease (example: chronic diarrhea, intestinal inflammatory disease), present gastrointestinal symptoms (example: diarrhea, vomiting), liver or kidney disease, or other known condition that may interfere in the absorption, distribution, metabolism, or excretion of the drug. Research participants with episodes of*

vomiting within 24 hours before the administration of the drug must be evaluated by the clinical investigator regarding the possibility of remaining in the study;

14- *Subjects with a history of cardiovascular disease, kidney, liver, metabolic, gastrointestinal, neurological, endocrine, hematopoietic (any type of anemia), mental illness or other organic abnormalities that could affect the pharmacokinetics of the product under study.*
15- *Any surgical or medical condition, including findings in the medical history or in the pre-trial assessments, that in the opinion of the investigator, constitutes a risk or a contraindication for the participation of the subject in the trial or that could interfere with the trial objectives, conduct or evaluation;*
16- *Has donated or lost more than 450mL or more of blood within three months previous to the study;*
17- *Has any condition preventing her of participating in the study according to the investigator's judgment;*
18- *Being vegetarian or have dietary habits that preclude ingestion of diet offered in the study;*
19- *The participant is inability to remain seated (approximately 90 ° plan) for 1 hour after drug administration of the drug, or time required at the discretion of the clinical investigator;*
20- *Being heavy smoker less 3 months;*
21- *Thyroid function tests outside normal limits (TSH, free and total T4, free and total T3);*
22- *Positive βHCG test for women;*
23- *Breastfeeding women;*
24- *Women who are taking contraceptives, because they have interaction when administered concomitantly with the drug in question;*
25- *Subjects requiring any prescription or non-prescription medications during the course of the study, including multivitamins, nutritional supplements and herbal products that may affect the outcome of the study, with the exemption of occasional use of paracetamol not exceeding 1000mg/day for maximum of three consecutive days;*
26- *Subjects who have been hospitalized for any reason within sixty days before the start of the study or who have been seriously ill within thirty days before the start of the study;*
27- *Subjects that have smoked tobacco, cigarettes or consumed coffee, snuff or drinks containing xanthines (coffee, tea, cocoa, chocolate, matte, cola, etc.) such as caffeine, theobromine, theophylline, or charcoal-grilled foods among others, affecting the pharmacokinetics of the drug in assessment, at least within 24 h before the start of the study;*
28- *Subjects who have intaked of grapefruit, orange, cranberry or juices of these 3 fruits, from 7 days prior to drug administration until collection of last PK sample in each period;*
29- *All cases where the principal investigator considers failure to the protocol and can make questionable the result of the study (severe adverse reaction or serious event adverse, Indiscipline of the subject, failure diet, if emesis occurs within the time set by the t_{max});*
30- *Unlikely to comply with the protocol requirements, instructions and trial-related restrictions; e.g., uncooperative attitude, inability to return for visits, and improbability of completing the trial;*
31- *Inability to communicate or cooperate with the investigator (e.g., language problem, illiterates, poor mental status) or to comply with the requirements of the entire trial, including dietary restrictions;*
32- *Subject is the principal investigator or any sub-investigator, research assistant, pharmacist, trial coordinator, other staff or relative thereof directly involved in the conduct of the trial.*

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6.6 Restrictions and prohibitions: before, during and after the study

1. *Always as possible, there should be avoided the use any kind of medication concomitantly with the study medication;*
   i. *Occasional use of paracetamol will be permitted within the screening period. The investigator may allow the subject to take paracetamol in case of pain during the trial, but the dose should not exceed 1000 mg/day for a maximum of three consecutive days. The amount of paracetamol administered must be recorded in the CRF. Any additional concomitant therapy that becomes necessary during the trial from the date of signature of informed consent and any change to concomitant drugs must be recorded in the corresponding section of CRF and in that case, the permanence of the subject in the study will be evaluated by the principal investigator.*
2. *Subjects should be non-smokers and will be instructed not to use any medication during the study and not to consume any alcohol, or xanthine-containing (coffee, tea, cocoa, chocolate, matte, cola, etc.) such as caffeine, theobromine, theophylline, or charcoal-grilled foods among others, affecting the pharmacokinetics of the drug in assessment within 24 hours before admission and through the study.*
3. *Chewing gum during confinement period;*
4. *The consumption of alcohol and energetic drinks will be prohibited in the 24 hours before the admission and through the study; Water will be permitted free except in the seven hours before and in the two hours after the administration of the medicine;*
5. *Ingestion of fried and fatty food during the confinement period;*
6. *To use food or drink that contains grapefruit (also known as toranja, pomelo, jamboa, laranja-melancia, pamplemusa, laranja-vermelha, laranja-romã) in the seven days before the beginning of each period up to the last collection of each period;*
7. *Soya and its derived can reduce the intestinal absorption of levothyroxine, so they are prohibited in the seven days before the beginning of each period up to the last collection of each period;*
8. *Procedures requiring use of iodinated contrast are prohibited in the 30 days before the beginning of the study;*
9. *To use vitamins or natural products (including garlic supplements) in the seven days before the administration of the medication until the last blood collection in each period of the study up to the last collection of each period.*

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6.7 Criteria for the discontinuation or withdrawal of participants from the study

The following criteria will be considered for the discontinuation of withdrawal of research participant from the study:

1. *Withdrawal of the subject's consent;*
2. *Occurrence of pregnancy;*
3. *Occurrence of adverse events leading the research participant to drop out of the study, such as unavailability or intolerance to the study procedures;*
4. *Adverse effects of the drug mentioned that are considered clinically significant by the physician in charge and/or harmful to the research participant's health;*
5. *Abnormal lab tests considered as clinical relevant;*
6. *Intercurrent diseases requiring medication;*
7. *Unfulfillment of the established rules;*
8. *Research participant present during the pre-admission (Period 1 or 2) tested positive for alcohol and/or drug test;*
9. *Research participant (for the women) present during the pre-admission tested positive for pregnancy test;*
10. *Chew the tablet during drug administration;*
11. *Study interruption;*
12. *Need to use some prohibited medication during the participation in the study;*
13. *To find out that the research participant does not meet the study requirements;*
14. *If the research participant take during the study any medication which contains the same substance which will be used as internal standard during the analysis of the plasma samples;*
15. *Research participant did not ingest the entire dose of the study drugs provided;*
16. *Research participant losing the last point of collection of the periods (period 1 or 2);*

17. *All cases where the principal investigator considers failure to the protocol and can make questionable the result of the study (severe adverse reaction or serious event adverse, Indiscipline of the subject, failure diet);*
18. *Unlikely to comply with the protocol requirements, instructions and trial-related restrictions; e.g., uncooperative attitude, inability to return for visits, and improbability of completing the trial;*
19. *In case of vomiting or diarrhea episodes after the administration of the drug until two times the Tmax of the active ingredient and/or metabolite, regarding the pharmaco mentioned, Levothyroxine, research participants having episode of vomiting or diarrhea within 08 hours after the administration must be excluded.*

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6.8 Definition of end of study

The end of study date will be the Last Subject Last Visit (LSLV) date. The trial will end when all randomized subjects who have received the IMP at least once, have completed/discontinued from the study as per trial protocol.
A clinical trial protocol may not be considered closed as long as:

- *Any subject is still receiving any investigation medicinal product (IMP).*
- *Visits specified by the protocol are still taking place.*
- *Procedures or interventions according to the protocol are still being undertaken in any subject.*
- *The post-treatment follow-up period, defined in the clinical trial protocol as being part of the trial, has not yet been completed for any subject.*

Any clinically relevant deviations from baseline findings for all subjects observed at end of trial examination have to be monitored until they have either returned to normal, are no longer considered clinically relevant, or can be explained.

In case of pregnancy All efforts should be made for postpartum follow-up and child development up to 1 year of age so that we can assess their psychomotor development. Any SAE experience during pregnancy must be recorded in the SAE Notification Form.

7 PPD / Site and form of confinement of the research participants

PPD

7.1 Site

Clinical Unit: PPD
Address: PPD
Phone: PPD

PPD

7.2 Form of confinement of the research participants

The healthy research participants will remain confined in the premises of Clinical Unit of PPD PPD *, under the responsibility of the medical team and under the care of the nursing team. For this study, will be selected 72 participants who will be admitted into two equally subgroups (36 participants in each subgroup divided equaly between gender and sequences). The participants will be received at around 7 p.m. on the day previous to the beginning of collections. On the day of drug administration, the nursing professional will start the routine procedures predicted for the participant during confinement including measurement of systolic blood pressure, diastolic blood pressure, heart rate, and temperature. The pharmacist in charge will release the medication following the list of randomization contained in the protocol (Annex 6), also providing to the nursing professional and the team involved in the collection of blood samples, the instructions related to the protocol. Therefore, the phlebotomists will install the heparinized intravenous catheters to perform the collections of sample zero (pre-dose) and those predicted throughout the day. The staff in charge for the collection will remain at the confinement site throughout hospitalization. There will be frequent visits of the nursing team to the bed where each participant is kept during the entire hospitalization period.*

8 PPD / Treatments of study

8.1 PPD / Test and comparator drugs

Tabela 1 – Medicamentos teste e comparador utilizados no estudo / *Test and comparator drugs*

Amostras Formulação Teste* / *Test Formulation samples**	
PPD / *Medication*	Eutirox®
PPD / *Manufacturer*	Merck, S.A. de C.V.
PPD *Address*	Darmstadt, Germany.
PPD / *Active ingredient*	PPD / *Levothyroxine sodium*
PPD / *Pharmaceutical form*	PPD / *Tablet*
PPD *Concentration*	
PPD / *Observations*	PPD PPD *Store at room temperature (15°C to 25°C). Protect from light and humidity.*
PPD / *Comparator Formulation samples**	
PPD / *Medication*	
PPD *Manufacturer*	Sanofi-Aventis Farmacêutica Ltda.
PPD / *Address*	Rua Conde Domingos Papaiz, 413 – Suzano – SP
PPD / *Active ingredient*	PPD / *Levothyroxine sodium*
PPD / *Pharmaceutical form*	PPD / *Tablet*
PPD *Concentration*	
PPD / *Observations*	PPD PPD *Store at room temperature (15°C to*

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e same batches of Test and Reference Drugs used in the Pharmaceutical Equivalence study must be mandatorily used.

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As predicted on Resolution – RE # 1170 dated 4/19/2006, the hospitalization can only be started after the issue of the conclusive report of pharmaceutical equivalence between test and reference formulations, and the content difference between the products is not higher than 5%.

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should be recorded on forms as Annexes 1 and 2, respectively, and they should be entered into the clinical report.

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8.2 Dosage

At every period, the research participant will receive orally a dose of 600mcg of Levothyroxine sodium corresponding to 03 tablets of test drug ***or*** *03 tablets of comparator drug according to the randomization list (Annex 6), together with 200mL of water after a fasting period of 8 hours. The participants will be instructed that the drugs under tablet form should be eaten whole, cannot break them or chew the drug and the oral suspension completely swallowed.*
After the administration of the drug the research participants must remain seated (approximately 90° position) during the 01 hour.

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8.2.1 Justification for dose

According to the local legislation RE1170, in general it is sufficient to carry out single-dose studies to determine Bioequivalence. Where it is not feasible to differentiate from basal concentrations after administration of a conventional dose, the administration of an increased single dose may be accepted in exceptional cases to allow appropriate quantification of the drug, provided that this dose does not exceed the maximum tolerated dose per day, which must be previously justified in the clinical protocol.
The FDA Guide - Guidance for Industry Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing, describes that a high dose of levothyroxine should be administered (600ug) to detect T4 above at baseline levels.
For this study, will be administer a dose of 600 µg (3 tablets of the 200 µg strength) for comparator and test product to ensure adequate pharmacokinetic determination, and accuracy measurement of the analyte.

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9 PPD

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9.1 Fasting and feeding times

The night before drug administration the research participants will go to the Clinical Unit of PPD *and must have their last meal until 11.00 p.m., and they will remain in fast un sing, which is estimated for the following morning.*

In order to maintain the standardization of the treatment groups, the diet (food and liquids) to be provided will follow the same standard, in two periods of confinement, for all research participants and must be free of fried and fat foods. To plan the menu, the nutrition professional will use as caloric reference the established in Ordinance # 193 dated 12/5/2006, article 5, paragraph 3 of the Worker Feeding Program ("PAT"). This way the meals provided will follow the following caloric quantities:

- *Main meals (lunch and dinner): must contain from 684 to 930 calories;*
- *Minor meals (snack): must contain from 300 to 400 calories;*
- *Minor meals (breakfast in extra collections and snack into 36 hours collection): must contain from 170 to 200 calories.*

The person in charge for the clinical step will provide the instructions to the Nutrition Service about the standardized diet that will be provided to the healthy participants, also highlighting the prohibition of the intake of beverages or foods containing caffeine or xanthines (black and mate tea, coffee, cocoa milk, cola sodas, guaraná, foods containing chocolate and others). The composition of the meals is on Annex 7.

Meal times:

- *Dinner - minimum of 8 hours of fasting;*
- *Lunch – 4 hours after the administration of the drug;*
- *Afternoon snack - 8 hours after the administration of the drug;*
- *Dinner - 12 hours after the administration of the drug.*

Liquids:

- *Water is allowed – until 7 hours before the administration of the drug and after two hours of the administration of the drug;*
- *Immediately after the administration of the drug – 200 mL of water;*
- *Prohibited ingestion of liquids – from 7 hours before the administration of the drug until two hours after the administration of the drug, except 200mL of water that will be given at the time of drug administration.*

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PPD *A scheme of the activities performed by the research participant in study periods 1, 2 and 3 is described on Table 2 below*:

PPD / *Table 2 - Activities performed by the research participant in study periods 1 and 2.*

PPD			
POOL	PPD *Before tration*	15mL	
C-1	-00:30 (PPD / *baseline*	7,5mL	
C-2	-00:15 (PPD) / *baseline*	7,5mL	
C-3	00:00**	7,5mL	PPD / *BP, pulse, temperature*
C-4	00:30	7,5mL	
C-5	01:00	7,5mL	PPD / *BP, pulse, temperature*
C-6	01:30	7,5mL	
C-7	02:00	7,5mL	PPD / *BP, pulse, temperature*
C-8	02:30	7,5mL	
C-9	03:00	7,5mL	PPD / *BP, pulse, temperature*
C-10	03:15	7,5mL	
C-11	03:30	7,5mL	
C-12	03:45	7,5mL	
C-13	04:00	7,5mL	PPD / *BP, pulse, temperature*
C-14	04:15	7,5mL	
C-15	04:30	7,5mL	
C-16	04:45	7,5mL	
C-17	05:00	7,5mL	PPD / *BP, pulse, temperature*
C-18	05:30	7,5mL	
C-19	06:00	7,5mL	PPD / *BP, pulse, temperature*
C-20	06:30	7,5mL	
C-21	08:00	7,5mL	PPD / *BP, pulse, temperature*
C-22	10:00	7,5mL	
C-23	12:00	7,5mL	PPD / *BP, pulse, temperature*

PPD			
C-24	24:00	7,5mL	PPD / *BP, pulse, temperature**
C-25	36:00	7,5mL	/ *BP, pulse, temperature**
C-26	48:00	7,5mL	/ *BP, pulse, temperature**
C-27	72:00	7,5mL	/ *BP, pulse, temperature**

PPD / *If necessary.
PPD / **5 minutes before drug administration.

9.2 Chronogram of sample scollection

*The collections will be performed through heparinized intravenous catheter inserted into a superficial vein of the research participant using 7,5mL tubes containing the anticoagulant **EDTA** and labeled with the number of participant, number of data collection, study period, the active code (LVT) and number protocol. After each blood collection, the catheter is washed with 1mL of sodium heparin.*
Before each collection the heparin solution inserted to wash the intravenous catheter will be removed.
Before the administration of the study drug (Period 1 and 2) a blood collection of 15mL (pool) that will be required for the validation of the analytical methodologies and will be used to constitute the plasma bank of all research participants for the preparation of the standard curves to be used during the study. In total will be collected 54 blood samples of 7,5mL and 2 blood samples each (pool) of 15mL, as established on Table 2. The total volume of blood including 15mL from screening and post-study will be of no more than 465mL of blood per participant.
Will be measured blood pressure, pulse and temperature of the research participant in the clinical evaluation pre-confinement and clinical evaluation of discharge from confinement. During in period of the confinement vital signs will be checked at pre-established times to Table 2. When the set time for measurement of vital signs coincide with the time of collection should be prioritized to collect blood, and accepted a range of ±30 minutes for the measurement of vital signs. Vital signs measured during the confinement period will be described in the report of the clinical study.
It is important to highlight that the research participant will be released hospitalization after of the 12 hours collection and they will return for the 24:00, 36:00, 48:00 and 72:00 hours. For the extra collections an interval of ± 1 hour of the actual time of collection described in the clinical protocol will be accepted. The extra collections held outside the range if ± 1 hour of provided time will be considered in clinical report as a deviation of protocol. For the collections held during the period of confinement, all delays and advanced shall be considered as deviation of protocol. The actual times of collection will be described in the Clinical Report.

9.3 PPD PPD *Procedures for the handling and storage of biological samples*

PPD

9.3.1 Internal transportation of biological samples

A professional from the samples processing lab will collect the tubes containing the blood sample of each one of the research participant, immediately after the collections. These samples will be placed in appropriate racks, inside a thermal box, containing solid ice and with temperature control (2 – 8°C).
The internal transportation of biological samples will be performed through ramps, whereas the research participant flow, clothes, food, and drugs distribution times must not coincide with the internal transportation of the biological samples.

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9.3.2 Identification of the samples

All the sample storage tubes must be labeled with the following information:

- *Research participant number (01);*
- *Collection number (C-02);*
- *Period of treatment (1 or 2);*
- *In cases of retain samples: (R);*
- *Active ingredient code (LVT);*
- *Biological matrix (plasma)*
- *Number of protocol.*

PPD

9.3.3 Handling and storage

Right after the collection, all the test tubes from the same time must be submitted to the Laboratory of Preparation of Biological Samples at the PPD clinical site, where they will be separated in racks and centrifuged at 3000rpm for 5 minutes, at about 4°C.
After centrifugation, using appropriate pipettes, plasma must be separated from sediment and distributed into storage tubes. Two storage tubes (tube containing the samples for analysis + tube containing retention samples) with approximate 2mL of plasma each will be frozen and stored in a freezer (-20°C) with temperature control. The maximum time between blood collection and the centrifugation of samples should not exceed 60 minutes and the time between the centrifugation and the storage of samples should not exceed 60 minutes, except the pool and the collection pre-dose (collection 1).
After frozen, the samples will be organized by study period and stored in plastic bags labeled with the protocol number, active's principle code, number of research participants and study periods (Period 1 or 2) and in the case of samples retains the description "R". Only if the samples destined to the analysis are submitted to the analytical unit of PPD.
The retention Biological samples will be stored in accordance with Resolution N° 441 of 12 May 2011 the National Health Council under the responsibility of PPD and will be discarded after the authorization of the sponsor.

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9.3.4 External transportation and submission of the biological samples from clinical step to analytical step

Samples should be placed in a properly identified Styrofoam box containing enough dry ice to maintain the freezing temperature of the samples. During transport the internal temperature of the Styrofoam box will be monitored by a calibrated thermometer.
The samples will be transported by own car and by a properly trained technician.
The samples for analysis will be transported followed by Delivery Check List and Biological Samples Checking (RQ-027) listing the box content, the number of samples and other information related to the study. The retention sample will stored at the center and can be shipped later when requested.
The person responsible for the analytical step must receive and check the samples immediately after receiving them, writing down the temperature at the moment of receipt and signing the Delivery Check List and Biological Samples Checking.

10 PPD / Adverse reactions and

10.1 PPD / Adverse events (AE)

PPD

10.1.1 Definitions

*An **Adverse Event (AE)** is an untoward medical occurrence harmful to health occurring in a clinical investigation participant who has received the drugs related to the investigation and has not necessarily a causal relation to the procedure and/or study drug.*

An AE may, therefore, be an unfavorable and non-intentional sign (including abnormal lab findings or vital signs), or a disease temporarily associated or not to the drug.

It is important to explain to avoid confusion, that the adverse events are classified according to their nature and intensity. Therefore, there are differences between ***Severe Adverse Event*** *and* ***Serious Adverse Event****. The definition of ICH topic E2A (Guide for Clinical Safety Data Management: Definitions and Standards for Expedited Reports) follows below for the differentiation of the terms "severe" and "serious":*
The term "severe" is frequently used to describe the intensity (severity) of a specific event (such as mild, moderate, or severe myocardial infarction); however, the event itself may be of relatively lower clinical importance (such as severe headaches). This definition is not the same for "serious", which is based on the event outcome for the patient/participant usually associated to events representing a life threat to the patient or him/her inability (as described above).
"Seriousness of the event" is not a synonym of "severity of the event".
This way we have:

- *Classification of Adverse reaction regarding its nature (serious and non-serious);*
- *Classification of the Adverse reaction regarding its intensity (mild, moderate, severe and lethal);*
- *Classification of the Adverse reaction regarding the study drug (suspected and non-suspected);*
- *Classification of Adverse reaction regarding frequency (once, continuous and intermittent)*
- *Classification of Adverse reaction regarding clinical outcomes:* recovered, not recovered, in recovery, recovered with sequel, worsening and death.

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10.1.2 Classification of Adverse reaction regarding its nature

*A **Serious Adverse Event (SAE)** is any untoward medical occurrence resulting in:*

- *Death;*
- *Life-threatening (the term life threatening refers to a reaction where the patient or participant is at risk of death at the moment the reaction occurs, it does not refer to a reaction that could have caused death, if it had occurred with a higher intensity);*
- *Persistent or significant disability/incapacity;*
- *Congenital abnormality/birth defect;*
- *Clinically important effect, including effects by use not indicated in the package insert or abuse (the term clinically important effect must be considered when a reaction is dangerous or requires intervention to prevent the other outcomes described in this definition);*
- *Requires patient hospitalization or prolongation of an already existing hospitalization (Hospitalization is defined as admission to a hospital site, even if for a period of less than 24 hours). The following hospitalizations are excluded:*
- *Treatment of a preexisting condition that is listed in the clinical history and has been planned before the study;*
- *Due to social problems;*
- *Established in the protocol as part of the study procedures;*
- *Emergency treatment of a participant for an event that does not meet the SAE definitions provided above and do not result in hospitalization;*
- *Elective (plastic surgery).*
- *Clinically important effect: the medical and scientific evaluation must be exerted in order to decide if other situations must be considered serious as the clinically important effects not leading to the patient's immediate death or life-treat or hospitalization, but that require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive care in a room or emergency room for allergic bronchospasm, blood dyscrasias, or seizure that does not result in hospitalization or development of drug dependence or drug abuse (ICH-E2A).*

Information about common adverse effects already known about the investigational product is described in the product pharmacology (item 1.3.5) and in the Informed Consent Form.

PPD

10.1.3. Classification of the adverse reaction regarding intensity

- *Mild: adverse event of little importance and short duration; may require treatment but does not substantially affect the normal life of the research participant;*
- *Moderate: an adverse event that alters the normal activity of the research participant, resulting in transient disability without sequelae, causes hospitalization, prolongation of hospitalization, attention in emergency service or absence from work;*
- *Severe: an adverse event that directly threatens the life of the research participant, causes congenital anomalies, results in permanent or significant disability, or requires intervention to prevent sequelae;*
- *Lethal: an adverse event leading to death.*

PPD

PPD / *Table 3 – Relation between adverse events and study drug.*

PPD / ***Suspected***	PPD *Temporal relation of the clinical event to the administration of the investigational products **makes a causal relationship possible**, and other drugs, therapeutic interventions, or essential conditions does not provide sufficient explanations for the event seen.*
PPD / ***Unsuspected***	PPD *Temporal relation of the clinical event to the administration of the investigational product **makes the causal relationship unlikely**, and other drugs, therapeutic interventions, or essential conditions provide sufficient explanations for the event seen*

PPD / *Table 4 - Classification of adverse event*

PPD / ***Once***	PPD / Adverse event occurred only once
PPD / ***Continuous***	PPD PPD *resolution between courses or treatment cycles.*
PPD / **Intermittent**	PPD PPD *The adverse event occurs and resolves during a cycle, course of treatment and then occurs again in another cycle, course of treatment.*

PPD

PPD

10.1.4 Classification of adverse reactions regarding the study drug

The clinical investigator will perform an evaluation of the adverse events after the verification of all accessible data and, if required, he/she will reevaluate the case when new information become available. The investigational products include the test drug under evaluation and the reference drug, that are given during any period of the study.
The investigator will judge, whether warranted or not, in his/her opinion, if the adverse event is related to the drug according to the following classification:

The investigator should report the evolution of the clinical outcome, considering the following evolution:

- Recovered;
- Not Recovered;
- In recovery;
- Recovered with sequel;
- Worsening;
- Death.

10.2. PPD / *Emergency procedures*

PPD

PPD

10.2.1 Procedures during the study

During confinement, in each study period, the participants will be followed by the healthcare professionals during all the period viewing the detection of adverse events, including signs of toxicity.

The participants will be instructed about the potential adverse events, as well as the need to inform them immediately to the investigator or his/her team.

Each participant will be requested to report any adverse event symptoms and it has occurred. The medical team will also be requested to notify the principal investigator if the use of additional medication has been required. Any adverse event occurring during the study period will be recorded according to item 10.3.

The questions performed to know if the participant has had some adverse event must be limited to general questions, such as: How are you?

Any adverse events occurring after hospitalization must be immediately informed to the team by any mean (telephone, personally, e-mail, etc.).

Upon blood collections, heart rate, blood pressure, and body temperature will be measured (according to Table 2).

Although there is no ICU in this unit, a mobile ICU will be on the alert during the performance of the study and an intensive care physician will be present to provide first aid. In case of the Levothyroxine Sodium the mobile ICU will be parked at PPD *available for the participants for 10 hours after the administration of the drug.* PPD PPD *will be qualified to perform emergency care and subsequent transfer to* PPD *which is located*

PPD *has the infrastructure to help and provide care to the usual complications whether se events of the drug mentioned. It also has a structure for first aid and an intensive care physician available.*

PPD

10.2.2 Post-study procedures

Upon discharge of the last hospitalization, all the participants will be warned once again that they must not donate blood or take part in any clinical trial with drugs, involving the collection of blood, for at least 6 months.
All the participants, including those who have withdrawn or have been excluded from the study after the administration of at least one dose of one of the drugs, must be clinically reevaluated (including vital signs, physical examination, and ECG) and have subsidiary lab tests similar to those performed on pre-study (except for serologica, and feces tests).
The participant who present altered results in the post-study examinations or any adverse event related to the study should be accompanied to the parameters return to normal or until the doctor feels irrelevant changes.
Regardless of the change, all the results obtained must be reported in the participant's case report form.
The negative or non attendance of the participant to perform these procedures, must be duly documented.

PPD

All adverse reactions occurred in the period between the signing of the Informed consent form until the time of completion of the clinical phase of the study, or until the issuance of test results post-study (or at the discretion of the clinical investigator) will be registered in the Non-Serious Adverse Event Notification Form (RQ-017) as in Annex 4, or whether the reaction is not related to study medication, and for the events considered as serious, they will be registered in Serious Adverse Event Form (RQ-018) as in Annex 5 and will be registered in the Clinical Report up to the date of its finalization.
The participant who has any adverse reaction (laboratory or clinical) will be followed until the reaction disappears.
The medical/disease conditions present before the beginning of the study will only be considered as adverse events if their status is aggravated after the participant inclusion. Abnormal laboratory values or test results constitute EA only if induce clinical signs or symptoms if they are clinically relevant or if they require treatment.
Once an AE is detected, it must be followed until its resolution or until it is considered permanent, and the evaluation must be performed at each visit (or more frequently, if required) to evaluate any change in severity, suspected relation with the investigational drug, the interventions required to treat them, and the results.

PPD

10.4 Notification of serious adverse event

Any adverse reactions or abnormal values of laboratory tests that are classified as serious occurring during the study will be reported immediately to the principal investigator, the sponsor of the study, the Ethics Committee (CEP) and ANVISA [CETER (Coordination of Therapeutic Equivalence) - and Pharmacovigilance Management] within 24 hours.

Recurrent episodes, complications, or progression of EAG initial monitoring shall be reported as the original episode, regardless of when the event occurs.

Any experienced SAEs after the final visit of the volunteer and for the duration of life insurance should also be notified if the investigator suspects a causal relationship with the drug under investigation.

PPD

10.5 Pregnancy

If pregnancy occurs after signing the consent form until the end of the study (completion of post-study studies) it should be reported to the Ethics Committee and registered with the Notification Form and Pregnancy Monitoring (RQ - 412), according to Annex 8. The PPD will route the participant to search for prenatal and PPD team will be following all the prenatal period until the bab birth.

For the research participants who eventually became pregnant (directly or indirectly) after the signing of the informed consent, a quarterly gestational follow-up will be required, as described below:

- *End of 1st quarter: preferably between the 12th and 16th weeks;*
- *End of 2nd quarter: preferably between 24th and 28th weeks;*
- *End of 3rd quarter: preferably between 36th and 40th weeks;*
- *Postpartum: preferably 15 to 20 days after* child-bearing*;*
- *In the first 6th month of the child's life;*
- *In the first year of the child's life.*

All efforts should be made for postpartum follow-up and child development up to 1 year of age so that we can assess their psychomotor development.

Any SAE experience during pregnancy must be recorded in the SAE Notification Form.

PPD

10.6 Life Insurance

For a period of 120 days, from the date of the 1st hospitalization, the participants will be covered by a life insurance, regarding eventual adverse events that might arise from the administration of the drug, and in cases of death and permanent disability, related or not to the clinical trial.

11 PPD

PPD

11.1 Basic principles

The study will be conducted according to the current version of the ICH/GCP – Guideline (CPMP/ICH/135/95) and according to the Declaration of Helsinki (1964) and its reviews of Tokyo (1975), Venice (1983), Hong Kong (1989), West Somerset (1996), Edinburgh (2000), Washington (2002), Tokyo (2004), and Seoul (2008) and Fortaleza (2013), as well as local regulations (Resolution 466/12 and 251/97 of the Brazilian National Board of Health - Ministry of Health, as well as Resolution RDC 016/07 by ANVISA).

The investigators are responsible for conducting the study in strict compliance to the approved protocol.

PPD

PPD

11.2 Ethics Committee (EC)

This protocol and the informed consent form will be submitted to the Ethics Committee registered on the Brazilian National Research Ethics Committee (CONEP) of CNS/MS for appraisal. The study will be conducted according to the Brazilian National Health Board - Ministry of Health (CNS-MS) Resolution 466/12. The study mentioned will only be started after the evaluation and approval of the Ethics Committee. All the corrections to this protocol must be approved by the Ethics Committee before applied, unless both in the investigator's and the physician's opinion, such delay would jeopardize the participant's health or life. If this risk is considered imminent, the investigator and the participant's physician may take all the actions considered of the best interest to the participant.

The Ethics Committee will have access, via Platform Brazil the curriculum of the researcher and the research project (Research Report) previously registered, the cover sheet signed and the Informed Consent Form. The sponsor and the Ethics Committee must be notified when and why such deviations from the protocol were required.

At the end of the research the PPD *will submit to the EC a copy of the Final Report.*

PPD

PPD

11.3 Informed Consent Form

The participants will receive an explanation of the nature and objectives of the study. It will be emphasized that the study is a research, and that the participant cannot wait that there is any therapeutic effect. The participant will also understand that he is free to withdraw from the study at any moment, with no obligation to provide the reason to do it and without any harm to he/she care at PPD

The participation of the par pants in the recruitment and screening activities will be followed by previous authorization according to the Recruitment Form. Once the participant's participation in the study is approved after an appropriate time for deliberation, each participant will be requested, if they agree, to sign the Informed Consent Form (Annex 3) to participate in the study, before hospitalization in the first period of treatment. It is a responsibility of the Clinical Investigator to obtain the signature of the Informed Consent Form. If the clinical investigator's responsibility to obtain the PPD *is designated to another team member, this designation must occur upon a proper instrument between the parties.*

at the Investigator in Charge opinion, a Protocol amendment changes substantially the study design or the risk the participants will be submitted to, the participants will be informed, and must sign a new consent regarding the decision to continue to participate in the study.

The informed consent form must comprise the changes and/or amendments, if any, presenting in its text only duly amended final information, in order not to confuse the participant.

PPD

11.4 Reimbursement

The participants will be reimbursed in the amount of R$ 870.00 (Eight hundred and seventy reals) regarding the expenses and time taken during the study.

It is important to highlight that, as this is a reimbursement for the time taken and incurred expenses, in case of withdrawal of the participant or absent in collections extras, this reimbursement will be proportional to the period the participant has participated in the study. The participant's participation in the screening process, regardless the approval or agreement to participate, will not be reimbursed.

PPD

PPD

11.5. Confidentiality

The records that could identify the participant will be kept confidential. However, lead researcher and team members will have access to original records of clinical participant data, to the extent permitted by law and regulations, in order to verify the procedures and test data, without violating the condition that information can't be disclosed. Auditors, the study sponsor and members of the Research Ethics Committee only have access to test results and medical history of the participants, but not to personal data. By signing the consent form Clarified, the participant is authorizing such access, even to give up the study.

12 PPD / Analytical methods

PPD

12.1 Description

The analytical methodology that will be used to determine the drug (Levothyroxine T4) in the plasma of the volunteers will be the high performance liquid chromatography (HPLC) using mass spectrometer (MS).

PPD

PPD

12.2 Validation of the analytical procedure

The validation of the analytical method is performed according to the Guide for Validation of Bioanalytical and Analytical Methods (RDC Resolution nº 27, dated 17/05/2012), through experimental studies that the method meets the requirements of analytical applications, ensuring the reliability of the results. Thus, the method should provide precision, accuracy, linearity, residual effect, matrix effect, selectivity, reproducibility, stability, according to the specifications of each test.

Thus, the equipment and materials must be properly calibrated, analysts must be skilled and trained and chemicals pharmacopoeia or properly characterized reference.

The following validation tests are performed:

- *Selectivity;*
- *Residual effect;*
- *Matrix Effect;*
- *Calibration curve;*
- *Precision;*
- *Accuracy;*
- *Recovery.*

To test the stability of the drug in biological fluid the following tests shall be performed in accordance with Resolution - RDC nº 27 of 17/05/2012:

- *Stability after freezing and thawing;*
- *Short term stability;*
- *Long term stability;*
- *Post-processing stability.*

It should also be tested for drug stability in solution for a period and storage conditions:

- *Stability of analyte and internal standard solution.*

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13 *Data analysis / Statistical methods*

The statistical phase of this study includes the choice of an experimental design adequate to the intra subject variability of the analyte in question (or its inter variability, if it is the case) and the adequate sample size determination.

The statistical methodology foresees the construction of at least two confidence intervals (CI_90%) for the ratio of the geometric means of the reference and test (1 and 2) treatments for the primary parameters (T/R), and a significance analysis of the fixed effects, adequate to the experimental design, through the application of the Variance Analysis technique (ANOVA). This last analysis aims exclusively to identify which factors would have greater influence in the answer, in case it had not been isolated as being a source of variation.

In this study it will be included the data of all participant who finished all the periods of the study. The points outlining the Plasma Concentration versus Time curve will only be reanalyzed if there is an analytical reason for doing so.

The Variance Analysis (ANOVA) model will include the terms sequence, formulation and period as fixed effects, and subject nested within sequence as a random effect. The sequence effect will be tested using the term subject nested within sequence as a term of the error with the level of significance of 10%.

The estimation to be obtained for the experimental error will be used in the construction of the confidence intervals for the final conclusion.

PPD

13.1. Sample size determination

*The sample size of a bioequivalence/relative bioavailability study (BE/BA) is determined through the calculation of the power function, which is based, among others factors, in an estimate of intra-subject coefficient of variation (**CV_{intra}**) obtained from the published literature data or by our previous experiences with the interested analyte.*
According to the previous studies performed at PPD *with levothyroxine using the reference drug Puran T4® in a crossover design, the CV_{intra} of primary pharmacokinetic parameters max,adj and AUC0-72,adj) vary from 20% to 40%, approximately. For the test treatment, it was informed that the CV_{intra} is around 24%.*
Therefore, using in a mean estimate of CVintra equals to 32% in a crossover 2x2 design, a significance level of 5% (α=0.05), assuming the normality among the individual difference of the primary pharmacokinetic parameters and a populational ratio between treatments of 95%, a minimum of 60 participants will be enough to achieve BE margins (80-125%) with 90% of power of test. Considering a dropout rate of 20% (12 participants), a total sample sample of 72 participants will be randomized in this study.
All calculations were made using the R software, PowerTOST package (R version 3.1.2, The R Foundation for Statistical Computing, 2014).

PPD

13.2. Efficacy analysis

Not applicable.

PPD

The pharmacokinetic parameters calculation will be processed in software WinNonlin 6.x (Phoenix) (standard) or in other case the necessary routines may not be contemplated in WinNonlin. Due to the fact that in the present study, endogenous substances are being evaluated, all pharmacokinetic parameters will be calculated considering the correction of the individual curves under treatment effect by the respective baseline levels found before administration of the drugs and also without correction. The correction is obtained by the difference of each concentration point of each subject/period and mean baseline levels (3 points before drug administration). Negative values will be replaced automatically by zero.

In the statistical report it will be presented the following information:

- *For each formulation: Tables with the individual plasmatic concentrations and their respective pharmacokinetic parameters (primaries and secondaries) with the descriptive statistics summarized at the end of each table (Arithmetic Mean, Standard Deviation, Minimum, Maximum and CV%);*
- *Mean Graphics of plasmatic Concentration versus time, in linear scale.*

13.3.1 PPD / *Pharmacokinetic Parameters*

PPD

$C_{max,adj}$: *Maximum plasmatic concentration reached, based in experimental data, directly obtained in the blood concentration curve versus time;*

$AUC_{0-72,adj}$: *Area under the plasma concentration versus time curve, from time to time within 72 hours of the last observed concentration above the lower limit of quantitation (calculated by the trapezoidal method).*

13.3.1.2 PPD / *Secondaries*

PPD

Tmax: *Time in which $C_{max,adj}$ occurs.*

PPD

C_{max}: *Maximum plasmatic concentration reached, based in experimental data, directly obtained in the blood concentration curve versus time;*

AUC_{0-72}: *Area under the plasma concentration versus time curve, from time to time within 72 hours of the last observed concentration above the lower limit of quantitation (calculated by the trapezoidal method).*

13.3.2 PPD / *Acceptance Criteria*

PPD . / *Table 4*

PPD /	PPD / *Data type*	PPD *means B/A*
$C_{max,adj}$	PPD	**80-125%**
$ASC_{0-72,adj}$	PPD	**80-125%**

Fonte: Resolução - RE n°1170 de 19/04/2006./ Source: Resolution - RE nº 1170 de April 19th, 2006.

PPD

13.3.3 Outliers considerations

In a Relative Bioavailability/Bioequivalence study in which crossover models are used, outliers are defined as those Participant (non-usual) who exhibit either an extremely high or low relative bioavailability for the reference formulation. The existence of an outlier without any protocol deviation may indicate one of the following situations:

a) Product failure: In this case an abnormal response may be present either for the test product or the reference product;

b) Subpopulation: This may occur when an individual represents a population in which the bioavailability of two products is notably different from the one observed in most population

In case there are outliers participant, their exclusion from the study should be clinically and / or analytic justified. The participant will not be excluded from the statistical analysis exclusively due to mathematical or statistical reasons. "It will be presented the results of the study with and without the inclusion of the outlier participant data, only if there is a relevant clinical or analytical reason that has not been defined in the protocol deviations and which is relevant in the final results assessment"

PPD

13.4 Pharmacodynamic analysis

Not applicable.

PPD

13.5 *Analysis of Other Endpoints*

Not applicable.

PPD

13.6 *Safety Analysis*

Not applicable.

PPD

13.7 *Interim Analysis*

Not applicable.

PPD

13.8 *Data monitoring committee*

Not applicable.

PPD

14 Acceptance criteria of the protocol deviation

Any protocol deviation will be widely discussed among the technical team, the Principal Investigator, the Sponsor and the Ethics Committee in Research. The deviation acceptance criteria should be described in the Final Integrated study Report that will be forwarded to ANVISA.

15 PPD / *Bibliographic reference*

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12. BRASIL. AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA. Resolução - RDC nº 31, de 11 de agosto de 2010. Diário Oficial da União, Brasília, 12 de agosto de 2010.

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PPD

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16 Annex

Annex 1: Retention samples
Annex 2: Inventory of drugs used in the study
Annex 3: Informed Consent Form
Annex 4: Non-Serious Adverse Event Notification Form
Annex 5: Serious Adverse Event Notification Form
Annex 6: Randomization List
Annex 7: Meals Composition
Annex 8: Notification Form and Pregnancy Monitoring

Annex 1 | Retention Sample

RETENTION SAMPLES

Medication:

According to Resolution RDC nº 31 issued on August 11st, 2010 and Resolution RE nº 894 issued on May 29th, 2003 for perform the equivalence and bioequivalence tests the laboratory responsible shall retain samples of test and reference medications in sufficient quantity to repeat the essay. Retention samples will be kept there one year after the validity date of the most recent product:

Medication	Name	Producer	Batch	Quantity bought by PPD	Retention Samples
Test					
Reference					

Biological samples:

The retention biological samples were stored at PPD in a -20°C freezer with daily temperature control and will be horize their discharge.

Annex 2 | Inventory of the medication used in the study

INVENTORY OF THE MEDICATIONS USED IN THE STUDY

All medications used will be registered, and their Brazilian Invoices will be stored.

It will be accomplished one verification control in conformity with the table below and this table will be inserted in the clinical report:

Number of units of the test and reference medication used in the study:

TEST MEDICATION	
Medication:	
Manufacturer:	
Address:	
Pharmaceuticals ingredients:	
Pharmaceutical form:	
Strengths:	
Batch number	
Total quantity acquired by PPD	
Quantity used by PPD	Equivalence: Pharmacy: Bioequivalence (Drugs consumed by the volunteers):
Loss	Equivalence: Pharmacy: Bioequivalence (Clinical Unit):
Quantity received by Pharmacy in the Clinical Unit	
Quantity returned to the Pharmacy in the Analytical Unit	
Total used by PPD	
COMPARATOR MEDICATION	
Medication:	
Manufacturer:	
Address:	
Pharmaceuticals ingredients:	
Pharmaceutical form:	
Strengths:	
Batch number	
Total quantity acquired by PPD	

Quantity used by PPD	Equivalence: Pharmacy: Bioequivalence (Drugs consumed by the volunteers):
Loss	Equivalence: Pharmacy: Bioequivalence (Clinical Unit):
Quantity received by Pharmacy in the Clinical Unit	
Quantity returned to the Pharmacy in the Analytical Unit	
Total used by PPD	

Annex 3 | Free and Informed Consent Form

FREE AND INFORMED CONSENT FORM- FICF

Research Title: Pharmaceutical bioequivalence evaluation of the pharmaco Levothyroxine sodium - Eutirox®200mcg (Merck, S.A. de C.V.) under tablet form versus Puran T4® 200mcg (Sanofi-Aventis Farmacêutica Ltda) under tablet form, in healthy male and female research participants under fasting conditions, using techniques Liquid Chromatography.

Main Investigator: PPD

You are invited to participate in a clinical research as a study participant (an individual who is priorly informed and consents to participate in a research voluntarily, or under the clarification and authorization of her/his legal responsible)**.**

Your participation is important, however, you should not participate against your will, and therefore, before agreeing to participate in this research, it is important that you read this consent form along with the team of PPD, as they will be able to assist you in clarifying completely the detailed nature of the research which you are being invited to participate, so that you understand the explanation of the proposed procedures. Your participation is voluntary (i.e., it depends on your willingness to participate) and you have the freedom to withdraw or discontinue participation in this clinical study at the moment you want.

This document is known as an informed consent form (ICF) and its name suggests that you should be able to decide whether or not to participate in the study only after having read and understood it.

Read carefully the information below and ask any questions you want, for all the procedures of this research are clarified.

I, _____, am being invited to participate in the clinical study mentioned above, which is under the responsibility of the physician PPD PPD and main investigator PPD.

STUDY OBJECTIVE

1. The study objective is to verify through a single dose study, if the test formulation of Levothyroxine sodium presents an equivalent rate and extension of absorption to the comparator formulation when administered with the same dosage and under fasting conditions and after baseline correction concentrations (baseline correction of thyroxine hormone that you already have in your body).

PROCEDURES

2. Pre-study (defined as the recruitment and selection period):

Before your participation in the study you were invited to come to PPD to check your health condition. Upon arrival at the center you signed the Recruitment Term that allowed the recruitment procedures that included medical evaluation, anthropometric data collection, and pre-study exams. So you've been

submitted to a thorough examination, checking pulse, temperature and blood pressure. You've been subjected to an electrocardiographic examination (examination of the heart). The doctor asked if you have or have had a disease and if you are taking any medication. Samples of Blood, urine and feces samples were collected for laboratory tests, including complete blood count (white blood cell count, erythrocyte), blood chemistries (blood glucose, total protein, albumin, transaminases, creatinine, urea, uric acid, alkaline phosphatase, total bilirubin and fractions, cholesterol and triglycerides), hepatitis B, hepatitis C, AIDS (HIV 1 and HIV 2) tests and urinalysic (urine I).

For your participation in this study, it will be necessary to perform the following tests: TSH (thyroid stimulating hormone), free and total T4 (Levotiroxin), free and total T3 for evaluation of your thyrodial function (gland responsible for production of two hormones T3 and T4).

On the day of admission, the following procedures will be performed:

Pregnancy test will be performed through urine dipstick testing upon patient's admission in the period 1 and 2.

At time of admission (Periods 1 and 2) the drug detection test will be performed through urine dipstick test and the alcohol detection test will be performed through the breathalyzer.

The following drugs can be detected in drug test: Methamphetamine, Opiate, Morphine, Tetrahydrocannabinol - THC (Marijuana/Cannabis), Amphetamine, Benzoylecgonine (cocaine), benzodiazepine.

Clinical evaluation for reassessment of your eligibility (if you are fit) to participate in the study.

Post-study (at the end of the study - after all procedures):

To check your health condition after you receive the drug, you will be subjected to an electrocardiographic examination (heart exam). Blood, urine and feces samples will be collected for laboratory tests, including complete blood count (white blood cell count, erythrocyte), blood chemistries (blood glucose, total protein, albumin, transaminases, creatinine, urea, uric acid, alkaline phosphatase, total bilirubin and fractions, cholesterol and triglycerides), pregnancy test for women.

The PPD will provide you with a copy of the results of the tests performed during the study.

3. You will be taking a medication that has a ***Levothyroxine sodium***, used in the treatment of hormone replacement and in the treatment of hypothyroidism.

4. During the study, you will participate three times for about ***24 hours***, with a minimum interval of ***65 days***. In each admission (period 1 and 2), in fasting condition***,*** you be taking ***600 mcg of Levothyroxine sodium***, which corresponds to ***3 tablets of one of the study drugs***, with 200ml of mineral water without gas. After administration of the drug you must remain seated (in the 90° position) for a period of 1 hour. You must ingest the whole medication and cannot break it or chew it.

In Period 1 you will receive the test drug or the comparator drug, in period 2 will be reversed, if you receive the test drug in period 1 you will receive the comparator drug in period 2 and vice versa At the end of the study you will have received 03 tablets of the test drug and 03 tablets of the comparator drug**.**

5. ***54*** blood samples of ***7,5mL*** for dose of medication will be collected, two samples of 15mL for validation of analytical methodologies and two samples of 15mL for laboratory tests and post-study will be collected through a needle inserted into a superficial vein. The total volume of blood will be approximately ***465mL***. At regular intervals and when necessary, your pressure, pulse and temperature will be checked. The minimum participation is estimated in ***76 days*** from the date of first admission, after the selection process.

6. It is important to emphasize that you will come to PPD for admission at 7:00pm on the day before drug administration and will be released after ***12 hours of drug administration***, returning to PPD for the collection of ***24:00, 36:00, 48:00 and 72 hours***. You will be observed throughout the study period and may contact the doctor on duty by the phone ***(62) 9299-6754 and / or (62) 3240-1900.***

The collections schedule is shown in the table below. During pre-dose collection (before drug administration), 01:00, 02:00, 03:00, 04:00, 05:00, 06:00, 08:00 and 12:00 hours and when required the vital signs (temperature, blood pressure and pulse) will be assessed (measured).

Day	Tempo (h)	Time of the day it will be collected
2nd	Pool Collection - Before the administration of the drug	**From 05:00 am**
	(-) 00:30 Collection	**Approximately at 06:30 am**
	(-) 00:15 Collection	**Approximately at 06:45 am**
	00:00 Collection – 5 minutes before the administration of the drug	**Approximately at 06:55 am**
	Drug Administration	**Approximately at 07:00 am**
	00:30 Collection	**Approximately at 07:30 am**
	01:00 Collection	**Approximately at 08:00 am**
	01:30 Collection	**Approximately at 08:30 am**
	02:00 Collection	**Approximately at 09:00 am**
	02:30 Collection	**Approximately at 09:30 am**
	03:00 Collection	**Approximately at 10:00 am**
	03:15 Collection	**Approximately at 10:15 am**
	03:30 Collection	**Approximately at 10:30 am**
	03:45 Collection	**Approximately at 10:45 am**
	04:00 Collection	**Approximately at 11:00 am**
	04:15 Collection	**Approximately at 11:15 am**
	04:30 Collection	**Approximately at 11:30 am**
	04:45 Collection	**Approximately at 11:45 am**

_____ _____ _____

Heading of Research Participant Heading of Physician Heading of main investigator

	05:00 Collection	**Approximately at 12:00 am**
	05:30 Collection	**Approximately at 12:30 am**
	06:00 Collection	**Approximately at 13:00 am**
	06:30 Collection	**Approximately at 13:30 am**
	08:00 Collection	**Approximately at 15:00 am**
	10:00 Collection	**Approximately at 17:00 am**
	12:00 Collection	**Approximately at 19:00 am**
3rd	24:00 Collection	**Approximately at 07:00 am**
	36:00 Collection	**Approximately at 07:00 pm**
4rd	48:00 Collection	**Approximately at 07:00 am**
5rd	72:00 Collection and Post Study Collection	**Approximately at 07:00 am**

7. You will remain fasting from 11:00 pm of the day you are admitted to the study at PPD until 4 hours after the drug administration. This means that you will get a dinner up to 11:00 pm of the day that you arrive at PPD, and will take the medication at around 07:00 am on the day after your arrival and will have lunch 4 hours after drug administration, i.e. by 11:00 am. So you will receive the medication after about 8 hours of fasting and will remain until lunchtime.

You will be served standardized meals (dinner, lunch, afternoon snack, dinner, breakfast and snack in the days of extra collections), drink only in prearranged times whereas after midnight (the day of arrival at PPD) you must remain without drinking water or any other liquid. The next day, you will receive 200mL of water with the medicine, and will only be allowed to drinking unlimited water 2 hours after drug administration.

STORAGE

8. The biological samples will be stored in accordance with Resolution No. 441 of May 12, 2011 of the National Health Council, which provides guidelines and conditions to be considered for storing biological samples, and will be used to verify through a single-dose study if the two formulations of Levothyroxine sodium 200mcg (being the comparator drug: Puran T4® 200mcg of the Sanofi-Aventis Farmacêutica Ltda. and the Test drug: Eutirox®200mcg of the Merck, S.A. de C.V.)are bioequivalent when administered at the same concentration and in fasting condition. Every new research will be submitted for approval of the CEP / CONEP system (National Committee for Research Ethics) and you must consent the use of these samples, by signing a new free and informed consent form.

9. Biological samples will be stored for non-commercial use, under the responsibility of PPD and management of the principal investigator and will be discarded after the consent of the sponsor.

10. Biological samples are stored in storage tubes identified by its research participant number with the aim of maintaining confidentiality and secrecy.

_____ _____ _____

Heading of Research Participant Heading of Physician Heading of main investigator

REQUIRED INFORMATION

11. You will be one of the ***72*** research participants divided into 02 groups of 36 participants each who will take part in this study.

12. You will receive all necessary information, including the benefits (see section "BENEFITS" below) and risks (see "POSSIBLE RISKS"), with conditions to consciously decide on the participation in this clinical trial.

Regardless of your will and permission, your participation in the clinical trial may be suspended due to:

a) Adverse events that are considered clinically significant by the treating physician and / or harmful to your health;

b) Occurrence of any disease, that at the physician's discretion, restricts your participation in the study;

c) Non-compliance with established regulations;

d) Any other reason that according to medical criteria is for your own or other participants' welfare;

e) The suspension of the study;

f) In case you need any prohibited medication during your participation in the study;

g) Finding out that you do not meet the study requirements;

h) Abnormal laboratory tests judged clinically significant by the physician;

i) In case you ingest a medicine containing the same substance that will be used during analysis of plasma samples during the study;

j) In case you eat and/or chew the tablet during drug administration;

k) You be hypersensitive (oversensitivity) to study medications or chemically related compounds;

l) If you are a vegetarian or have dietary habits that preclude the intake of the diet offered in the study;

m) In case you don't attend the last collection of the periods;

n) In case of women, present at the time of admission (Period 1 or 2) a positive pregnancy test result;

o) You present during the pre-admission (Period 1 or 2) testing positive for alcohol and/or drug test;

p) You have thyroid function tests (free and total TSH, total and free T4 and TSH) outside normal limits;

q) You do not ingest the 200mL of water during the administration of the drug;

_____	_____	_____
Heading of Research Participant	Heading of Physician	Heading of main investigator

r) You use any prescription or non-prescription medications during the course of the study, including multivitamins, nutritional supplements and herbal products that may affect the outcome of the study, with the exemption of occasional use of paracetamol not exceeding 1000mg/day for maximum of three consecutive days;

s) If you present episode of vomiting or diarrhea within 8 hours after drug administration.

RESPONSABILITIES

13. In order to be able to participate in the clinical trial, you should be in good health condition, and cannot be under any medical treatment or taking any kind of drugs or medication. Your collaboration is important in the following points:

- ✓ You cannot have any drugs or alcohol dependency;
- ✓ Remain seated (approximately 90 °) for 1 hour after administration of the drug or the time required at the discretion of the clinical investigator;
- ✓ Do not be a smoker within 3 months;
- ✓ You should avoid the use of other concomitant medications with the study medication whenever possible. In case you need to use some medication, you should contact the staff of the PPD;
- ✓ You must not have donated blood or plasma within the three months preceding the study.
- ✓ You must not have participated in any experimental study or ingested any experimental drugs within the six months preceding the beginning of the study
- ✓ You must not consume alcohol beverages in the 24 hours before admission to the study until the last sample collection of each period is performed;
- ✓ Do not smoke tobacco, cigarettes, or consumed coffee, snuff or ingested beverages containing xanthines (coffee, tea, cocoa, chocolate, mate, cola, etc.) such as caffeine, theobromine, theophylline or charcoal grills, among others in the 24 hours before the start of the study until the last collection of each period;
- ✓ Do not eat or drink grapefruit (also known as toranja, pomelo, jamboa, laranja-melancia, pamplemusa, laranja-vermelha, laranja-roma), orange and cranberry in the 07 days before the beginning of each period up to the last collection of each period;
- ✓ You must not consume chewing gum during the admission period;
- ✓ You must not consume vitamins or natural products [including garlic supplements (derived from garlic and onion)] in the 7 days prior to drug administration until the last sampling of each study period;

_____	_____	_____
Heading of Research Participant	Heading of Physician	Heading of main investigator

- ✓ Do not consume soy and its derivatives in the 7 days prior to administration of the drug until the last collection of each study period;
- ✓ Do not perform procedures that require the use of iodinated contrast (the iodine base) within 30 days prior to the start of the study.
- ✓ You must attend study visits on the appointed dates and times;
- ✓ You must remain fasting for the predicted time;
- ✓ Take all the medication provided;
- ✓ Follow the suggested diet;
- ✓ Ingest liquids in set times;
- ✓ In the case of women, do not use hormonal contraceptive methods;
- ✓ Return to PPD at the appointed date, time and place for the consultation and discharging appointment.

BENEFITS

14. Your participation in this study is experimental, and it does not have the purpose of subjecting you to a treatment.

By participating in this study you will be assessed and monitored by a qualified medical staff in addition to performing a careful and detailed clinical evaluation, including clinical and laboratory examinations, which will attest if you are healthy.

Your participation is very important and thus will contribute effectively in ensuring the quality of the medication offered to the general population.

POSSIBLE RISKS

15. The administration of medications can cause side effects, anaphylactic (allergic) reactions and other serious unpredictable, and in some cases, cause death.

You should understand that the participation in this study involves risks that may be unexpected, related or unrelated to the study. Risks associated with blood collection in your arm may include: pain, hematoma (bruise), bleeding at the site where blood was withdrawn, dizziness, fainting and, on rare occasions, infection.

The blood sampling for prolonged times, through a single vein may lead to its inflammation (thrombophlebitis), with pain and local swelling (when applicable).

_____	_____	_____
Heading of Research Participant	Heading of Physician	Heading of main investigator

The risks associated with this medication side effects are:

Very common reaction (≥ 1/10)
Common reaction (≥ 1/100 and < 1/10)
Unusual reaction (≥ 1/1.000 and < 1/100)
Rare reaction (≥ 1/10.000 and < 1/1.000)
Very rare reaction (< 1/10.000)
Unknown reaction (cannot be estimated from the available data)
In general, the adverse reactions of levothyroxine are associated with an excessive dosage and correspond to the symptoms of hyperthyroidism.

- **Heart disorders**

Very common: palpitations.
Common: tachycardia.
Unknown: cardiac arrhythmias and angina pain.

- **Skin and subcutaneous disorders**

Unknown: rash, hives and sweating.

- **Psychiatric disorders**

Very common: insomnia.
Common: nervousness.
Unknown: excitability.

- **Musculoskeletal and connective tissue disorders**

Unknown: muscle weakness and cramps, osteoporosis in suppressive doses of levothyroxine, especially in postmenopausal women, especially when treated for a long period.

- **Vascular disorders**

Unknown: hot flashes, circulatory collapse in preterm low birth weight infants.

- **Disorders of the reproductive system and breast**

Unknown: menstrual irregularities.

- **Gastrointestinal disorders**

Unknown: diarrhea and vomiting.

- **Investigations**

Unknown: weight loss.

- **Nervous system disorders**

Very common: headache.
Unknown: tremors, benign intracranial hypertension particularly in children.

- **General disorders and administration site conditions**

Unknown: heat intolerance, fever.

- **Endocrine disorders**

Common: hyperthyroidism.
Such effects generally disappear with reduced dosage or temporary withdrawal of treatment.

16. Additional risks, unusual or unexpected side effects or previously unreported discomforts may occur. Thus, it is important that you tell the study doctor or a staff at PPD who is in charge of your treatment about all the symptoms and side effects you have, either if you think or not this has been caused by the study medication.

17. Women of childbearing potential: use of study medication may involve unknown risks to a pregnant woman, an embryo, fetus (unborn baby) or child being breastfed. So, if you suspect pregnancy, or if you're planning to become pregnant or are breastfeeding, you cannot participate in this study.

In order to reduce the risk of pregnancy, you should use an effective method of contraception (to prevent pregnancy) while participating in this study . If you are already using a contraceptive method you should talk to the team of doctors at PPD to ensure that its use is considered acceptable in this study. No method to prevent pregnancy will be imposed on you . You can choose the most appropriate method , after discussing it with the team of PPD doctors. Some types of birth control include oral contraceptives (pills) or barrier methods such as condoms or diaphragm . If you do not have sex as a lifestyle choice (eg, sexual abstinence for religious reasons or otherwise) , it will be accepted as a method of contraception . In this case , you do not need to use another method . Also, if you have sex without reproductive risk , it will not be necessary to use a contraceptive method . Your personal decision will be respected . However, if during the study you become sexually active with intent / ability to become pregnant , you should inform the study doctor immediately. Along with the study doctor you will be able to decide what is the best contraceptive method, which will be provided at no cost to you .

The pregnancy test will be performed in the pre-study phase, before each admission period (Period 1 and 2) and after the admission to the 2nd period . The results of the pregnancy test should be negative for you to be able to continue participating in this study.

If you become pregnant during the study, you should notify PPD staff immediately. In case this happens, you will be withdrawn from the study for safety reasons and will receive full assistance, including medical care for your needs as a mother and to your baby (since conception).

WITHDRAWAL, DISRUPTING AND DISMISSAL

18. Your participation in this study is voluntary (i.e., just depends on your willingness to participate), having the freedom to give up when you want without any explanation. If you give up, you should immediately notify your decision to the physician or researcher in charge.

19. Your withdrawal, disrupting or dismissal from the study will not cause harm to your care and medical treatment (comprehensive care) by PPD staff.

CONFIDENTIALITY

20. The records that might identify you will be kept confidential. PPD will not identify you at the time of publication of results.

_____	_____	_____
Heading of Research Participant	Heading of Physician	Heading of main investigator

However , the main investigator and team members have access to the original records of your clinical data to the extent that is permitted by law and regulations, in order to verify the procedures and test data , without violating the condition that your information can not be disclosed . Auditors, study sponsor and the members of the Research Ethics Committee will only have access to the results of your examinations and your medical history , but not to your personal data . By signing this Consent Form, you authorize such access, even if you withdraw from the study.

The clinical study to which you are being invited to participate can have the results published in newspapers **and / or** magazines **and / or** scientific articles. If that is the case, the confidentiality of your records that perhaps can show your identity will be protected. In case of any publication, it will respect the rules of privacy and confidentiality in accordance with applicable standards.

INTERCURRENCES

21. In any medical complication arising, directly or indirectly, from your participation in this research, you will immediate and comprehensive care, whose costs will be borne by the sponsor or Research Center PPD responsible for the clinical study that you are participating. It is therefore very important that if you have any unusual symptoms, discomforts Unusual, unexpected or non-reported previously, you look IMMEDIATELY PPD medical staff.

In the period between signing the Consent Form (the moment you accepted the invitation to participate in this clinical study) and study completion (last collection of the study), PPD will be responsible for any supplying of medication, which manages without any cost to you.

22. During a period of 120 days from the date of the 1st hospitalization, you will be covered by a life insurance policy in relation to possible adverse events that may have stemmed from the administration of the drug and in cases of death and permanent disability, related or not to the clinical study.

23. It is also important that the sponsor and the Research Center PPD responsible for the clinical study will be responsible for any and all necessary cost in relation to any adverse events that you may suffer as a result of their participation in the study.

COMPENSATION

24. By participating in this study, after sample collection post-study, you will be reimbursed in the amount of R$ 870,00 (Eight hundred and seventy reals), concerning expenditure and time spent during the course of clinical study (reimbursement is the material compensation, exclusively expenditure of the research participant and their companions, when necessary, such as transportation and food). The relinquishment or waiver before attending for the first hospitalization is not entitled to compensation, or if you attended only part of the study you will be reimbursed proportionally.

_____	_____	_____
Heading of Research Participant	Heading of Physician	Heading of main investigator

CLARIFICATION OF DOUBTS

25. You can contact PPD Research Ethics Committee for complaints regarding the trial by calling the number ***(62) 3240-1906.*** PPD CEP (Ethics Committee) business hours are ***Monday to Friday from 8:00 am to 12:00 pm.***

26. You have the freedom to contact PPD to receive additional information related to research or to your rights as a research participant. PPD has a 24 hours telephone answering service to assist you. Phones: PPD ***and / or*** PPD ***.***

27. The Institute of Pharmaceutical Sciences will keep you informed, in a timely manner, whenever there is any additional information and will provide any clarification regarding the progress of the research, as per your request.

All your biological material will be identified uniquely and unmistakably to maintain the confidentiality of your identity and as accept the invitation to participate in this clinical study you authorize the storage, use and disposal of this biological material and the principal investigator, team members involved in this clinical study, auditors, sponsor of the study, the Research Ethics Committee responsible for approving the project to access your health information under the same established conditions. You also authorize the publication of the results of this clinical study in magazines, newspapers and books, when necessary.

After reading this term and clarify all your doubts, you, the responsible researcher and physician shall write your initial on all the pages, and you and the doctor responsible for applying the term shall sign the respective fields. After signing both copies of the document, you will receive one and the other will be filed at PPD.

By signing this consent form I have not renounced any legal right that I will have to participate in this clinical study.

I have read carefully this Consent form, after having the opportunity to ask questions about its content, receiving explanations about the study and all of my questions have been answered completely. I am also sure that all the information provided, including my medical history, is true to the best of my knowledge, and I declare that I have received a signed and dated copy of this document.

I hereby give my consent voluntarily and accept the invitation to participate in this clinical study.

_____	_____	_____
Heading of Research Participant	Heading of Physician	Heading of main investigator

Signature of the research subject:_____

Aparecida de Goiânia, ___/___/___.

PLEASE DATE AND SIGN IT AT THE SAME TIME

Dactyloscopic Printing (when applicable):

* Signature of impartial witness (1): _____

* Applicable in cases where the research subject cannot read, understand and sign this document.

Aparecida de Goiânia, ___/___/___

PLEASE DATE AND SIGN IT AT THE SAME TIME

***** Signature of impartial witness (2): _____

* Applicable in cases where the research subject cannot read, understand and sign this document.

Aparecida de Goiânia, ___/___/___.

PLEASE DATE AND SIGN IT AT THE SAME TIME

Doctor's Signature*: _____

Aparecida de Goiânia, ___/___/___.

PLEASE DATE AND SIGN IT AT THE SAME TIME

*** The physician responsible for the study or other doctor for this delegate are able to sign this document**

TELEPHONE CONTACTS:

Investigator responsible for the Clinical Phase: PPD - Phone: PPD – 24 hours

Main investigator: PPD - Phone: PPD

Nursing Staff – Phone: PPD – 24 hours

Research Ethics Committee of the Institute of Pharmaceutical Sciences – Phone number: PPD PPD The CEP's (Ethics Committee) business hours are Monday to Friday from 8:00 am to 12:00am.

Institute of Pharmaceutical Sciences - Clinical Unit - Phone: PPD

_____	_____	_____
Heading of Research Participant	Heading of Physician	Heading of main investigator

Annex 4 | Non serious adverse event notification form

PPD	**ADVERSE EVENT NOTIFICATION FORM NON-SERIOUS**	Document Code: **RQ 017**	**Revision: 012**
		Page 1 of 1	

1. Protocol:	2. Nº Vol/Group:	3. Date of last administration:
4. Period:	5. Code treatment:	

6. Description of treatment:

7. Date of Birth:	8. Age:	
9. Gender:	10. Height:	11. Weight:

12. Description of the adverse event:

13. Beginning Date Hours

( ) Before administration of medication of the study ( ) After administration of medication, during the confinement ( ) After having been discharged from confinement ( ) Post study exams	Signature and stamp of the physician responsible:

Summary prescription

14. Date	15. Medication	16. Dosage	17. Adm. via	18. Time	19. Indication	20. Responsible

21. Evolution:

22. Prevision in Protocol	23. Intensity:	24. Causal Relationship:	25. Conduct	26. Frequency	27. Evolution
( ) Expected ( ) Unexpected	( ) Light ( ) Moderate ( ) Severe	( ) Suspect ( ) Not suspect	( ) Obsevation ( ) Hospitalization ( ) Terapeutic ( ) Pharmacological ( ) Other	( ) Only one ( ) Intermittent ( ) Continuous	( ) Recovered ( ) Recovered with sequelae ( ) Unknown ( ) Not recovered ( ) Fatal ( ) In monitoring

28. Conclusion

( ) Opening *	Signature and stamp of the physician responsible:

* If event Opening to be monitoring to RQ 118 or RQ 267
*N.A. = Not apply

Annex 5 | Serious adverse event notification form

1. Protocol:	**2. Volunteer/Group Number:**	**3. Code treatment:**
4. Description Treatment:		
5. Period:	**6. Date of last administration:**	
7. Date of Birth:	**8. Age:**	**9. Sex:**
10. Volunteer´s Identification:	**11. Height:**	**12. Weight:**

13. Date of the event: _____/_____/_____ **14. The event is a result of pregnancy?** ( ) Yes ( ) No

15. Beginning: _____:_____ **16. Ending:** _____:_____

17. Description of the Serious Adverse Event:

18. Result of the Serious Adverse Event:

- ☐ Hospitalization
- ☐ Permanent Disability
- ☐ Life threatened
- ☐ Patient´s death
- ☐ Overdose
- ☐ Others Clinically Significant events

19. Relationship with the product under investigation:

- ☐ Suspect
- ☐ Non-Suspect

20. Evolution

- ☐ Recovered
- ☐ Recovered with sequelae
- ☐ Not recovered yet
- ☐ Unknown
- ☐ Fatal

21. Condition of product´s investigation

- ☐ Without alterations
- ☐ Discontinued
- ☐ Reduced
- ☐ Interrupted

22. Concomitant medication:

Medication: _____ Pharmaceutical Form: _____

Indication: _____

Administered Dosage: _____ **Via:** _____ **Frequency:** _____

Beginning: ____/____/_____ **Ending:** ____/____/____.

23. Additional medication:

Use additional pages and put them in annex. Are there pages annex? ( ) yes ( ) no.

24. Treatment of the adverse effect without medication, specify:

25. Was the protocol interrupted?

( ) Yes
( ) No

In case it was, specify the responsible.
Date of the interruption: _____/_____/_____
Name of the product under investigation: _____

26. In case of death

Date of the death:_____/_____/_____

Cause of the death: _____

Was the death certificate obtained?
☐ Yes ☐ No ☐ Pending

Has na autopsy been performed?
☐ Yes ☐ No ☐ Pending

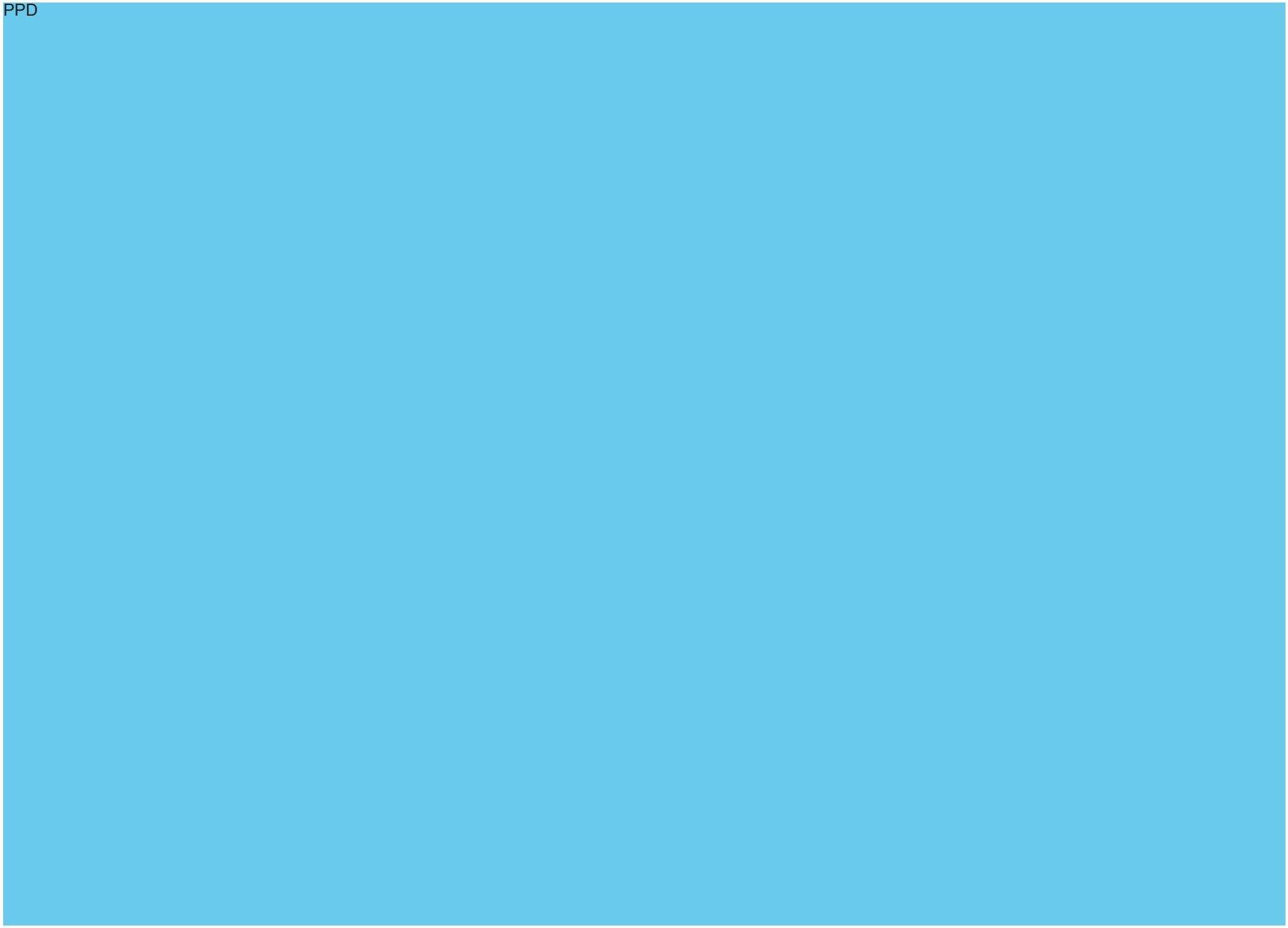
In case it hás, was a copy of the autopsy result obtained?
☐ Yes ☐ No ☐ Pending

Summarized notification: (Annex additional pages if necessary)

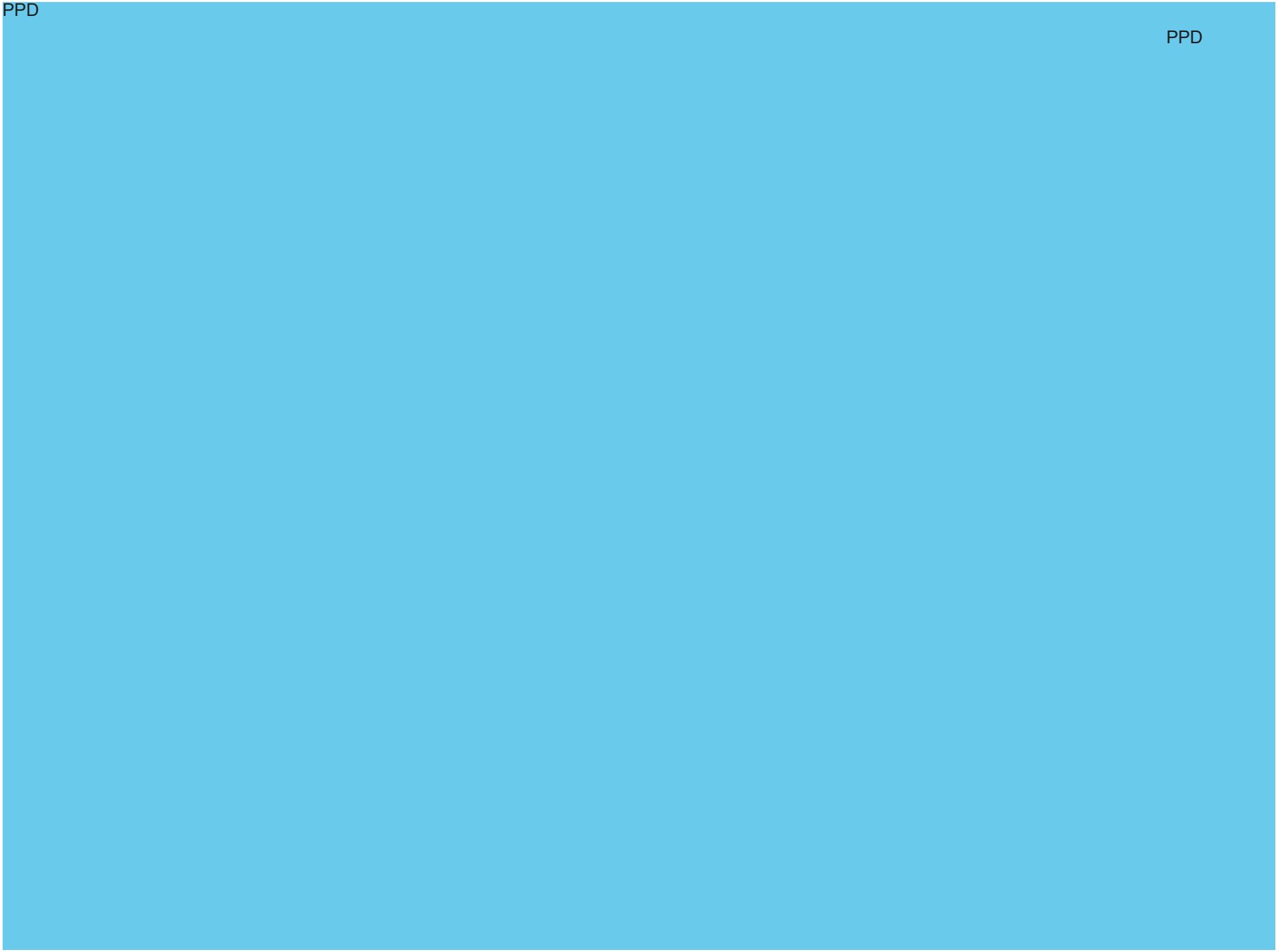
Medical doctor responsible for the Notification:_____

Professional registration:_____

Annex 6 | Randomization list


PPD


PPD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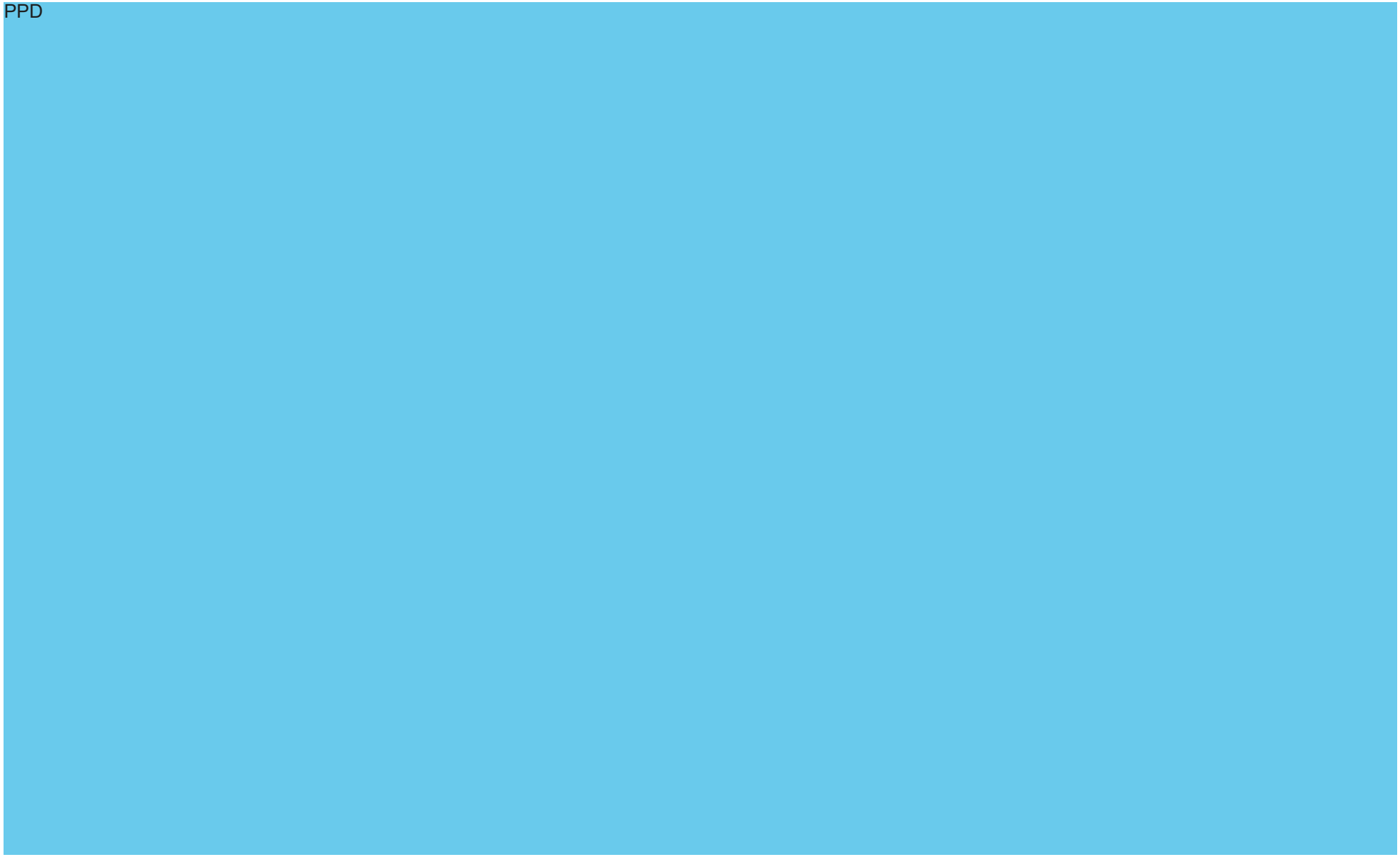
PPD


PPD

Annex 7 | Meals composition

Protocol: PPD
Medication: Levothyroxine Sodium
(Merck)
Standardized meals provided during the study

Date:	**1st day**	
Arrival dinner up to 11:00 p.m. (684 - 930) kcal		
Contents	**Amount**	**Calories**
Rice	02 portions	234 - 290 Kcal
Beans	02 portions	50 – 80 Kcal
Meat	02 units	210 - 290 Kcal
Vegetable	01 portion	95 -145 Kcal
Green Salad	01 portion	45 - 65 Kcal
Fruit	01 unit	50 - 60 Kcal
Date:	**2nd day**	
Lunch starting at 11:00 a.m (684 - 930) kcal		
Contents	**Amount**	**Calories**
Rice	02 portions	230 - 290 Kcal
Beans	02 portions	50 - 80 Kcal
Meat	02 units	210 - 290 Kcal
Vegetable	01 portion	95 -145 Kcal
Green Salad	01 portion	45 - 65 Kcal
Fruit	01 unit	50 - 60 Kcal
Afternoon snack starting at 03:00 p.m. (300 – 400) kcal		
Contents	**Amount**	**Calories**
French bread with ham and mozzarella	01 unit	275 - 362 Kcal
Refresh	01 glass	25 - 38 Kcal
Dinner starting at 07:00 p.m. (684 - 930) kcal		
Contents	**Amount**	**Calories**
Rice	02 portions	230 - 290 Kcal
Beans	02 portions	50 - 80 Kcal
Meat	02 units	210 - 290 Kcal
Vegetable	01 portion	95 -145 Kcal
Green Salad	01 portion	45 - 65 Kcal
Fruit	01 unit	50 - 60 Kcal
Date:	**3rd day**	
Breakfast starting at 7:00 a.m. (170 – 200) kcal		
Contents	**Amount**	**Calories**
Snack	02 units	80 – 100 Kcal
Juice	01 glass	90 – 100 Kcal
Date:	**3th day**	
Snack starting at 7:00 9.m. (170 – 200) kcal		
Contents	**Amount**	**Calories**
Snack	02 units	80 – 100 Kcal
Juice	01 glass	90 – 100 Kcal

Date:		4th day
Breakfast starting at 7:00 a.m. (170 – 200) kcal		
Contents	**Amount**	**Calories**
Snack	02 units	80 – 100 Kcal
Juice	01 glass	90 – 100 Kcal
Date:		**5th day**
Breakfast starting at 7:00 a.m. (170 – 200) kcal		
Contents	**Amount**	**Calories**
Snack	02 units	80 – 100 Kcal
Juice	01 glass	90 – 100 Kcal

Annex 8 | Notification Form and Pregnancy Monitoring

1. Protocol:
2. Randomization number:
3. Date of last administration:
4. Treatment (s) administered:
5. Last menstrual period (LMP):____/____/____
6. I was using contraception? ( )YES ( )NO what? _____.
7. Discovery date of pregnancy: ____/____/____
8. Gestacional age at the time of exposure to study drug: ( ) weeks or ( )1st quarter ( ) 2nd quarter ( )3rd quarter
9. Is conducting prenatal care? ( )YES ( )NO
10. Current weight: _____ Blood pressure:_____

11. include information about medications used, laboratory and clinical examinations, complaints, hypertension, diabetes:

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12. Medical history of subject (include personal information or family risk factors or known conditions that may affect the development of pregnancy, ex .: hypertension, eclampsia, diabetes, including gestational diabetes, infections during pregnancy, occupational and environmental agents that may be risk factors, genetic factors, consanguineous disease - specify the degree of relatedness in events):

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13. Obstetric history:

( ) Primigravida ( ) Multigesta ( ) Number of Pregnancies ( ) Natural childbirth ( ) Caesarean ( ) abortion ( ) curettage

Others (molar pregnancy, ectopic pregnancy, twins etc):_____

_____

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Responsible for initial notification: _____ **Date:** ___/___/____

14. Follow-ups visit: (Include information about prenatal care, current weight, blood pressure, medications used, laboratory and clinical examinations, complaints, hypertension, diabetes and pregnancy outcome) - enter all the data in the lines below. If necessary, add sheets to this page.

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15. Final outcome of pregnancy:

Date of end of pregnancy: ___/___/___

( ) Birth to the term ( ) Premature birth ( ) Stillbirth * ( ) Miscarriage * ( ) Induced abortion

( ) Unknown

Gestational age at birth in weeks (if known):_____

*Complete RQ018- Serious Adverse Event Notification

16. Development of the conceptus:

( ) Normal ( ) Congenital anomaly ( ) others neonatal problems ( ) Unknown

Birthweight: _____kg Height at birth: _____cm Cephalic perimeter: ____cm

Thoracic perimetec: _____cm Apgar; ( )01 minute ( ) 05 minutes

Responsible:_____ **Date:**___/___/___