PROTOCOL	
TITLE:	Post-approval observational prospective study to evaluate the prevalence of the metabolic syndrome in prostate cancer patients both before and after a 12-month treatment with quarterly LHRH analogue formulations (ANAMET Study).
PROTOCOL CODE:	IPS-TRI-2008-01
COMMERCIAL DRUGS:	Quarterly LHRH analogues currently in the market: -buserelin (9.45 mg quarterly implant; SC injection) -goserelin (10.8 mg quarterly implant; SC injection) -leuprorelin (22.5 mg quarterly injection; SC injection) -leuprorelin (22.5 mg quarterly injection; IM injection) -triptorelin (11,25 mg quarterly injection; IM injection)
RESPONSIBLE FOR THE PROJECT:	PPD Medical adviser
SPONSOR:	IPSEN PHARMA S.A. Ctra. Laureà Miró 395 08980 Sant Feliu de Llobregat Emergency contact: PPD PPD Phone: PPD Fax: PPD
FINAL DATE:	Final version: 9 July 2008

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1. SYNOPSIS

Sponsor's Identification and Address	IPSEN PHARMA, S.A. Avda. Laureà Miró, 395. 08980 Sant Feliu de Llobregat (Barcelona). Phone: 93 685. 81.00 Fax: 93 685.10.11
Study Title	Post-approval observational prospective study to evaluate the prevalence of the metabolic syndrome in prostate cancer patients both before and after a 12-month treatment with quarterly LHRH analogue formulations (ANAMET Study).
Protocol Code (according to official coding standards)	IPS-TRI-2008-01
Co-ordinating Investigator and his/her Address	PPD Hospital Vall d' Hebron Passeig de la Vall d' Hebron 119-129 08035-Barcelona
Type of Centres where the Study is Anticipated to be Carried Out	The study will be carried out at the Urology and/or Radiation Therapy Services of different hospitals throughout the Spanish territory.
Evaluating ECCR	Hospital Vall d'Hebron's ECCR
Primary Objective	The objective of this study is to assess the prevalence of the metabolic syndrome in accordance with the NCEP ATP III Panel definition in patients with prostate cancer both before and after 12-month treatment with quarterly LHRH analogue formulations.

Design	ANAMET is a post-approval observational, prospective, multicentre and open study to assess the prevalence of the metabolic syndrome in patients with prostate cancer both before and after 12-month treatment with quarterly LHRH analogue formulations.
Disease or Disorder Studied	Male prostate cancer patients.
Data of the Studied Drugs	The patients included in the study will receive treatment with LHRH quarterly analogues. The LHRH analogues commercialised in our country are: - buserelin (9.45 mg quarterly implant; SC injection), - goserelin (10.8 mg quarterly implant; SC injection), - leuprorelin (22.5 mg quarterly injection; SC injection), - leuprorelin (22.5 mg quarterly injection; IM injection), and - triptorelin (11.25 mg quarterly injection; IM injection).
Study Population and Total Number of Subjects	Patients diagnosed with prostate cancer and scheduled to receive a long-term (12 months) treatment with LHRH quarterly analogues. **Inclusion Criteria** - Patients should give their written informed consent (personally signed and dated) before starting with any study-related procedures. - Patients should be 18 years old or over. - Patients should have a histology-confirmed prostate cancer diagnosis, and be eligible for either continuous androgen deprivation therapy or treatment with LHRH analogues in accordance with the specifications of the relevant data sheets for a period of at least 12 months.

	- Patients should have an estimated survival expectancy of at least 12 months in the investigator's opinion. **Exclusion Criteria** Any patient currently on or having previously received androgen deprivation therapy.
Schedule	Inclusion of the first patient is foreseen to take place on the first quarter of 2009, and treatment completion by the last patient is foreseen to occur on the first quarter of 2011.
Financial Sources	As the sponsor of the study, IPSEN PHARMA, S.A will meet all expenses originated by same.

2. TABLE OF CONTENTS

3. GENERAL INFORMATION

Code

IPS-TRI-2008-01

Title

Post-approval observational prospective study to evaluate the prevalence of the metabolic syndrome in prostate cancer patients both before and after a 12-month treatment with quarterly LHRH analogue formulations (ANAMET Study).

Data on the Sponsor/the Monitor

IPSEN PHARMA, S.A.
Avda. Laureà Miró, 395. 08980 Sant Feliu de Llobregat (Barcelona).
Phone: 93 685.81.00 Fax: 93 685.10.11

The staff from the IPSEN PHARMA, S.A.'s Medical Department will be responsible for monitoring the observational study.

Centres and Autonomic Communities where the Study is Anticipated to be Carried Out

The study shall be carried out with the participation of urologists and radiation therapists from different hospitals throughout the Spanish territory.
Annex 7 to this protocol shows the interim list of Autonomic Communities, centres and principal investigators of this study.

Foreseen Length

The first patient is foreseen to be included in the study on the first quarter of 2009, and the last one on the first quarter of 2010. The last patient is foreseen to complete the study on the first quarter of 2011.

4. STUDY RATIONALE: CRITICAL REVIEW OF LITERATURE

4.1 Review of the Disease

4.1.1. Prostate Cancer

Prostate cancer is currently considered one of the most frequent cancers in men (first in incidence and third in mortality) (1). Most of the cases are localised cancers at the time of diagnosis, and so apt to be adequately treated with surgery and/or radiation therapy (brachytherapy, external-beam radiation therapy, etc.).

More than one third of them appear in locally advanced stages, notwithstanding the screening campaigns. These patients, generally with stages T3 (capsule involvement, vesicle involvement), T4 (nearby organ involvement), N+ (nodal involvement) or M+ (distant, basically bone, involvement), will be candidates to treatment with either complete or partial hypothalamic-pituitary axis blockade.

Indications for hormone blockade are the following: a) as the first option in systemic disease; b) as adjuvant following curative pelvic-prostatic radiation therapy for 2-3 consecutive years; c) as neoadjuvant prior to a 6-month radiation therapy treatment.

Two/three-year treatment concomitant to radiation therapy yields 5- and 8-year disease-free survival rates of around 78% in high-risk locally-advanced disease (Gleason histological grade equal to or higher than 8, PSA > 20 ngr, T equal to or higher than 3, N +, M0).

Treatment with LHRH agonists is not devoid of adverse reactions. In some cases there is a transient exacerbation of the clinical symptoms (basically bone pain) when treatment starts. Some cases of worsening of a preexisting haematuria, or urinary obstruction and/or a sensation of weakening or paresthesia of the lower limbs have been described with the LHRH analogues at treatment initiation. These symptoms are generally transient and they disappear on the first or the second week without requiring treatment discontinuation. In any case, the possibility of an initial symptom exacerbation should be born in mind when treating neurologically affected patients or patients suffering from urinary obstruction.

The following adverse reactions have been described during the treatment: hot flushes, pain at the site of injection, erectile dysfunction and transiently elevated arterial blood pressure that resolves spontaneously.

There are, however, other potential adverse reactions that could be considered significant and that have not as yet been studied in depth, such as the effect of castration (a consequence of the treatment with LHRH analogues) on the patient's metabolic profile.

4.2 Literature Review

Androgens participate decisively of the male body composition. Serum testosterone concentrations are positively correlated to the muscular mass, and negatively to the body fat. In prostate cancer, changes in the body composition are deemed to be the adverse effects of androgen deprivation, although the effects of such deprivation have not been well defined as yet. In a study in which the effects of GnRH agonists on patients with locally advanced prostate cancer, with either positive nodes or recurrent prostate cancer were studied, weight and fat mass gain was appraised. However, weight loss and the disease symptoms before

starting the treatment made it difficult to determine whether the body composition changes were due to hypogonadism or to a treatment-related symptom improvement (2).

To this date, all the studies carried out on androgen deprivation and the development of the metabolic syndrome have been retrospective (4, 5, 6, 7, 8 and 9), or else performed on a reduced number of subjects (11).

5. OBJECTIVES

5.1. Primary Objective

The objective of this study is to assess the prevalence of the metabolic syndrome according to the NCEP ATP III Panel definition in men with prostate cancer both before and after a 12-month treatment with quarterly LHRH analogues formulations.

5.2. Secondary Objectives

Modifications of the parameters below at the baseline visit, at 6 months and at 12 months will be assessed as secondary objectives:

- Physical exploration:
  i. BMI
  ii. Blood pressure
  iii. Weight
  iv. Abdomen perimeter

- Laboratory tests:
  i. HbA1c
  ii. Haemoglobin
  iii. Triglycerides

iv. Total, LDL and HDL cholesterol
v. PSA
vi. Total testosterone
vii. Glycaemia
viii. C-Reactive Protein

6. SOURCE OF INFORMATION AND SCOPE

This study will be conducted according to the usual clinical practice, on patients with prostate cancer who will be submitted to continuous androgen deprivation therapy for at least one year.

7. STUDY DESIGN

Definition of the Study Population: Selection Criteria

This study will include patients diagnosed with prostate cancer who are scheduled to receiving long-term treatment (12 months) with quarterly LHRH analogues.

All patients will be evaluated by means of the following inclusion and exclusion criteria:

· Inclusion Criteria

In order to be eligible for this study, the patients should satisfy the following criteria:

- Give their written informed consent, (personally signed and dated) before starting with any study-related procedures.
- Be 18 years old or over.
- Have a histology-confirmed prostate cancer diagnosis, and be eligible for either continuous androgen deprivation therapy or treatment with LHRH

analogues in accordance with the specifications of the relevant data sheets for a period of at least 12 months.

- Have an estimated survival expectancy of at least 12 months in the investigator's opinion.

· Exclusion Criteria

Patients satisfying any one of the following criteria will not be eligible for the study:

- Being administered or having previously been administered with an androgen deprivation therapy.

Observation Period

The observation period for each patient will be 12 months.

Treatment Description and Definition of Exposure

Patients on treatment with quarterly LHRH analogues over 12 months due to prostate cancer, in accordance with the indications described in the products' data sheets.

Also, all patients will receive anti-androgen treatment for one week before and two weeks after receiving the first injection of LHRH analogues.

Concomitant Treatments

All concomitant medications, particularly those treating significant aspects of the metabolic syndrome, such as hypolipemiating, anti-hypertensive, hypoglycaemiating, etc. agents, should be reported. Any dietary or physical activity modification experienced by the patients during the 12-month follow-up should also be reported.

Selection of the Control Group

Not applicable.

Previous Determination of the Sample Size

We assume that the prevalence of the metabolic syndrome (MS) among patients at study initiation will amount to 30%, and that it will increase a further 2% during the study. Increase of over 5% is considered clinically significant.

If we assume that the increased prevalence of the metabolic syndrome will be less than 5%, that 1% of the subjects with baseline MS will not show it at the end of the study, and having established an alpha value of 5%, 500 patients are necessary to have a statistical power of 80%. If we assume 10% of dropouts, 556 subjects are necessary.

8. VARIABLES AND MEASURING INSTRUMENTS. MEASUREMENTS DEFINITION AND DESCRIPTION

8.1. Primary Objective Measurement Variables

The parameters described by the NCEP ATP III Panel for the diagnosis of metabolic syndrome will be applied. Three or more parameters must be above the upper limits for the following variables:

1. Abdominal obesity (abdomen perimeter) > 102 cm
2. Triglycerides ≥ 150 mg/dL
3. HDL-cholesterol < 40 mg/dL
4. Blood pressure ≥ 130/85 mmHg
5. Fasting glycaemia ≥ 110 mg/dL

8.2. Secondary Objective Measurement Variables

- Physical exploration:
  - BMI
  - Blood pressure
  - Weight
  - Abdomen perimeter

- Laboratory tests:
  - HbA1c
  - Haemoglobin
  - Triglycerides
  - Total, LDL and HDL cholesterol
  - PSA
  - Total testosterone
  - Fasting glycaemia
  - C-Reactive Protein

8.3. Adverse Event Recording

Any adverse events experienced by the patients in the course of the study will be recorded.

8.4. Study Visits

8.4.1. Baseline Visit (Month 0)

The patients should be explained the programme in detail before entering the study. Additionally, the following will be obtained and recorded:

- Patients will be confirmed to satisfy all inclusion and exclusion criteria
- Patients will sign the informed consent
- Demographic variables: initials, date of birth, race
- Current clinical history: including the prostate cancer current stage and the treatments received up to the moment of entering the study
- Record of concomitant medications
- Record of concomitant diseases
- Physical examination: including systolic and diastolic blood pressure determination (all the investigators shall use the same model of sphygmomanometer), measurement of the abdominal perimeter (all the investigators shall use the same tape measure), and weight
- Analytical determinations: Glycaemia, HbA1c, Haemoglobin, Lipid profile: total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides), Thyroid hormones (TSH), PSA, Total testosterone and C-Reactive protein
- Assessment of Metabolic Syndrome
- Record of the treatment with quarterly LHRH analogues
- Record of adverse events considered to be associated with the LHRH analogues, including local tolerability of the injection

8.4.2. Follow-upVisits (Month 6 and Month 12)

The following information should be collected and recorded in the CRFs at each visit:

- Physical examination: including measurement of systolic and diastolic blood pressure, measurement of the abdominal perimeter, and weight
- Analytical determinations: Glycaemia, HbA1c, Lipid profile including: total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides), Thyroid hormone (TSH), PSA, Total testosterone and C-Reactive protein
- Record of concomitant medications
- Assessment of Metabolic Syndrome
- Record of treatment with quarterly LHRH analogues
- Record of adverse events considered to be associated with the LHRH analogues, including local tolerability of the injection

8.5. Study Termination by a Patient

Some of the reasons why a patient should terminate the study are described below:

- Patient withdraws his consent.
- Investigator's decision.
- Patient transferred or lost to follow-up.
- Adverse event.
- Lack of adherence.

If a patient dropped out from the study, the reasons should be recorded in the CRF.

8.6. Study Termination

Ipsen has the right to terminate this study at any time. The reasons leading to such termination include, but are not limited to, the following:

- The incidence or the severity of adverse events either in this study or in other studies are indicating potential risks for the patients.
- The recruitment is not sufficient to satisfy the objectives of the study.
- The primary and/or secondary objectives of the study have been reached.

8. STATISTICAL CONSIDERATIONS

8.1. Classification and Definitions of the Subjects of the Study

Pre-selected centre:	Centre requested to participate in the study and verified to be currently following-up patients who might be candidates to entering the study (this involves both participating and not-participating centres)
Participating centre:	Centre that has accepted to participate in the clinical study and completed the patients screening records
Participating subject:	Subject who has been thoroughly informed about the study and who has given his/her written informed consent for participation (prior to initiating any of the study procedures)
Treated subject:	Participating subject treated with at least one dose of the study drug

Subject who has completed the study:	Treated subject who has completed all of the study assessments
Dropout:	Treated subject who has not completed the study and/or the treatment

8.2. Definitions of Analysis Populations

Included and treated population:	All treated subjects
Complete population:	All treated subjects paying the Month 12 end visit

9.2.1. Analysis Populations

The primary analysis will be performed on the whole of the population, Additionally, the analysis will be repeated on the included and treated population.

Analysis of the safety data will be performed on the treated population.

9.2.2. Subject Allocation and Reasons for Exclusion from Analyses

The instructions for allocation of subjects to each of the analysis populations will be defined and documented in the course of a data review meeting.

Those subjects in whom one or more of the violations and/or deviations below occurs may be excluded from analysis:

- violation of the inclusion and/or exclusion criteria
- having received no study drug whatsoever
- not adhering to the study drug as they should

- taking banned medications
- committing deviations regarding treatment administrations
- having had no initial or post-initial assessment of the primary results

8.3. Sample Size Determination

If we assume:

1) metabolic syndrome (MS) prevalence = 30% at study initiation,

2) that such prevalence will increase by 2% along the study,

3) that 5% of prevalence increase is clinically not significant,

4) that alpha = 5% (unilateral) and power = 80%, and that we mean to demonstrate that the increase of MS prevalence will be lower than 5% (non-inferiority study)

Using 500 subjects, the upper limit of the unilateral confidence interval (CI) observed of 95% will be expected to be lower than 0.050 with a power of 80% when the expected difference, pT - pS, D1, is 0.020 and the proportion of discordants, h = p10 + p01, is 0.070, and the proportion yes in both cases, p11, is 0.290. The results are based on 5000 simulations that used the Newcombe-Wilson's score method to produce the confidence interval (Newcombe RG (1988): *Improved confidence intervals for the difference between binomial proportions based on paired data*. Statistics in Medicine 17:2635-2650).

Considering a 10% dropout rate, the final sample size is 500/0.9 = 556 subjects. The recruitment of 556 subjects from some 60 Spanish centres has been devised. Each of the centres will be requested to enlist them following a chronological order based on the date of the first visit carried out at the centre.

Assuming this sample size, the MS prevalence will be estimated with a precision of 0.038 (for a 5% bilateral alpha).

9.3.1. Significance and Estimation Test

A bilateral confidence interval of 90% will be calculated for the difference between prevalence rates of the Metabolic Syndrome at study initiation and at study completion (study initiation subtracted from study completion) according to the Newcombe's method (difference between two proportions based on paired data using Newcombe's method 10, 1998c). If, and only if, the upper limit of the confidence interval is lower than the upper limit of the equivalence region <+ 5 %>, prevalence after the study will be demonstrated to be no worse than prevalence at study initiation.

8.4. Statistical/Analytical Methods

The statistical analyses will be performed by a Contract Research Organisation (CRO), managed by the Sponsor's Head of Biostatistics and the Commercialised Products Data Management.

A statistical analysis plan (SAP) will be prepared as a separate document to fully describe the planned statistical analysis, including table templates, figures and printouts (TFP).

Statistical evaluation will be performed with the assistance of the Statistical Analysis System (SAS)® (version 8 or higher).

9.4.1. Selection of the Centres and Selection of Patients

Summarised descriptive statistics will be provided (n, mean, standard deviation [SD], median, minimum, maximum) or else frequency counts of the data collected

in the course of the centre selection process (characteristics of all pre-selected services gathered through a pre-selection visit: geographical location, type of service -Urology or Radiation Therapy-, number of patients treated yearly with LHRH analogues, in order to be able to categorise the services over the base of their size) with the aim of documenting the suitability of the selected centres (and also the reasons for not participating).

Summarised descriptive statistics will be provided (n, mean, standard deviation [SD], median, minimum, maximum) or else frequency counts of the data collected in the patients' screening record (key characteristics of the screened patients population: year of birth, sex, year in which prostate cancer was diagnosed and, in the case of not-included patients, the reason of not inclusion) with the aim of documenting the suitability of the selected patients (and also the reasons for not having selected the remaining ones).

Each service may include 10-12 patients (which is a mean over the base of the number of active services). Since ours is a competitive clinical study, a service could include a greater number of patients with a maximum 30 subjects.

9.4.2. Demographic and Other Characteristics at Baseline

Summarised descriptive statistics will be provided (n, mean, standard deviation [SD], median, minimum, maximum) or else frequency counts of the demographic and baseline data regarding the total populations included / treated.

9.4.3. Final Destination of Subjects and Withdrawals

Numbers and percentages of the subjects recruited and included in each population will be tabulated by centres. The reasons for excluding subjects from each of the populations will also be tabulated. Additionally, the numbers of subjects treated, subjects who discontinued their medication and subjects who

completed the study will be tabulated. A table showing the main reasons for discontinuation of the study drug will also be prepared.

9.4.4. Evaluation of Efficacy

As stated in section 8.1., the primary variable will be the prevalence of the Metabolic Syndrome according to the ATP III Panel definition, i.e. the presence of three or more risk factors, as shown by the table below:

Table II.6-1. Clinical Identification of the Metabolic Syndrome *

Risk Factor	Level of Definition
Abdominal obesity	Abdominal perimeter† > 102 cm
Triglycerides	≥ 150 mg/dl
HDL-cholesterol	< 40 mg/dl
Blood pressure	≥ 130/85 mmHg
Fasting glucose	≥ 110 mg/dl

* The ATP III Panel found no suitable evidence for recommending that the usual insulin-resistance determination (e.g. plasma insulin), the proinflammatory status (e.g. high-sensitivity C-reactive protein) or prothrombotic status (e.g. fibrinogen or PAI-1) be performed for diagnosing the metabolic syndrome.

† Some men may have many metabolic risk factors even when their abdominal perimeter is just slightly enlarged, e.g. 94 – 102 cm. The resistance to insulin in those persons may have a strong genetic component. A change of habits may be beneficial to them and also to those men with a far more enlarged abdominal perimeter.

The difference between Metabolic Syndrome at baseline and at study completion will be calculated, and also the 90% confidence interval associated to it in accordance with paired data. Newcombe's method 10, 1998c, will be used with this purpose. If the CI's upper limit were lower than 5%, it may be concluded that a clinically not significantly increased prevalence of SM was found in the study.

The secondary parameters are: BMI, Blood pressure, Weight and Abdominal perimeter.

Regarding secondary parameters, statistics will only be issued including confidence intervals based on the raw data from every evaluation; the analyses will be stratified as per the status of the Metabolic Syndrome.

9.4.5. Evaluation of Safety

All the safety data will be included in the subjects' data lists. Tabulated analyses and summaries will be based on the general population.

As this is a non-interventional study, only treatment-related Adverse Events (AEs) will be recorded. The AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA), using the term and the organic system class preferred by MedDRA. The AE lists shall be submitted by subject, organic system class and preferred term.

The incidence of all treatment-related emergent AEs (TRAEs) and all SAEs reported will be tabulated. Additionally, tabulated summaries according to maximum severity, relationship with the drug and also AEs/TRAEs associated with early withdrawal of the study medication will be submitted.

TRAE is defined as any AE occurring during the active phase of the study, provided that:

- it had not occurred before receiving the first dose of study drug, or

- it had occurred before receiving the first dose of the study drug but its severity increased in the course of the active phase of the study, or

- it had occurred before receiving the first dose of the study drug, its severity was the same but its relationship to the study drug was established in the course of the active phase of the study.

Treatment-related emergent AEs shall be marked with (*) in the lists of AEs.

Concomitant medication will be coded according to the WHO Drug Dictionary, and summarised including the number and percentage of subjects receiving concomitant medication as <drug class and preferred drug name>.

The statistical summary (mean, median, SD and interval, if applicable) will be displayed by treatment group and also overall regarding heart rate determination and laboratory tests at each assessment, and the changes occurred from baseline will be highlighted. As to the analytical data (including Fasting glucose, HbA1c, Haemoglobin, Triglycerides, Total cholesterol, LDL-cholesterol, HDL-cholesterol, Thyroid hormones (TSH), PSA, Total testosterone, C-Reactive protein), the data printouts will point out at the abnormal values, with a list of those that may be significantly abnormal. Time-progress tables of the amount and percentage of subjects with low, normal or high values or with either normal or abnormal exams will be displayed.

8.5. Analysis of Subgroups

Overall descriptive statistics of all of the parameters, and also according to the MS status at the time of entering the study, will be provided.

8.6. Interim Analyses and Data Monitoring

No interim analyses are foreseen.

9. ETHICAL ASPECTS

The CRO will be responsible for Data Management under Ipsen's supervision. In this study, information will be obtained by means of a specifically designed CRF. The information collected will be confirmed to be accurate, consistent and verifiable, through the application of standardised practices and procedures.

Risk-Benefit Assessment for the Research Subjects

Since the patients will receive treatment with LHRH analogues with strict adherence to the indications of the safety sheet on prostate cancer, neither additional benefits nor additional risks to those already known are foreseen. It is expected, however, that a study like the current one will be able to provide very valuable information (in addition to the epidemiological one) on the drug safety within the routine clinical practice for this group of patients, and also improved management and monitoring of androgen deprivation.

9.1. Patient Information Sheet

The Investigator should make sure that the patient is duly informed on the protocol through the Patient Information Sheet and through the information supplied by the Investigator him/herself.

Before including a patient in the study, the physician should obtain the patient's informed consent to participate.

9.2. Confidentiality of the Data

With the aim of guaranteeing confidentiality, the patients will be identified on the CRF by their initials and their date of birth only.

According to European Directive 95/46/CE on the protection of persons regarding personal data processing, and Spanish Law 15/1999 on Personal Data Protection, patients' personal data will be confidential and delivery of such data to third parties who are different from those already mentioned is specifically prohibited, with the only exception of the existence of a signed agreement among all the interested parties.

Should the patient request so, medical information will be provided to his/her family doctor or to the health professional responsible for his/her welfare.

All the information generated by this study should remain available for inspection by Ipsen's authorised staff, by the local and national authorities, by the Personal Data Protection Body or by the Ethics Committees.

9.3. Interference with Prescription Practices

Only patients strictly satisfying the indications for LHRH analogues, and who in the Investigator's opinion will obtain a benefit from the treatment, will be included in the study.

11. PRACTICAL CONSIDERATIONS

11.1. Work Plan

Patient's informed consent should be available before undertaking any study-related assessment.

The investigators to participate in ANAMET should meet the requirements below and/or provide Ipsen with the following information:

- Information on the centre:

  Name, position, address, telephone and fax numbers of the principal investigators and of the collaborating investigators, the study co-ordinators or any other staff responsible for the study conduct at the centre.
- Having signed an agreement with reference to ANAMET (by the centre or by the Investigator, as applicable) in which the participation of the Investigator in the study is mentioned.
- Having obtained the relevant Ethic Committees and Autonomic Communities approvals.

Patients will be controlled on an outpatient basis throughout the study.

The performance of the study is schematised as follows:

STUDY SCHEME

	Baseline (V0)	Month 3	Month 6 (V2)	Month 9	End Visit Month 12 (V3)
Inclusion/Exclusion Criteria	+				
Informed Consent	+				
Demography	+				
Case history and concomitant diseases	+				
Blood pressure	+		+		+
Abdominal perimeter	+		+		+
BMI, weight, height	+		+		+
Prior and concomitant medication	+		+		+
Laboratory tests*	+		+		+
Treatment	+	+	+	+	+
Adverse Events	+		+		+

* **Laboratory tests:** Glycaemia, HbA1c, Hb, Lipid Profile (Total, HDL and LDL cholesterol, and triglycerides), Thyroid hormone (TSH), C-reactive protein, PSA and Total testosterone.

11.2 Procedure for Recording and Notifying Adverse Reactions

Every adverse reaction, independently of its severity and of its suspected relationship with the study drug, should be recorded in the relevant section of the Case Report Form.

The Investigator should let the Sponsor know any severe adverse reaction within a maximum 24 hours following his/her own awareness of same.

The Sponsor must report the suspected severe adverse reactions to the Competent Authorities within a maximum 15 calendar days from learning about the adverse reaction.

11.2.1 Adverse Reactions Record

Adverse reaction: Any response to a drug that is harmful and unintended, and occurring at normally-administered doses to humans for prophylaxis, diagnosis or treatment of diseases, or for the restoration, correction or modification of physiological functions. The term also includes all harmful clinical consequences of the dependence, the abuse and the wrong use of drugs, including those consequences caused by drug use under conditions that are not those for which the medicine has been approved, and the ones caused by misadministration (RD 1344 / 2007).

Each investigator will be responsible for evaluating any adverse event (be it spontaneously reported by the patient or objectively detected following a medical questioning) occurring in the course of the study.

If, in the Investigator's opinion, there were or there could be a causal relationship with the study drug and consequently the adverse event were labelled as adverse reaction, the Investigator should state so in the specific form within the Case Report Form (CRF), and report:

- ⇨ date of onset,
- ⇨ length,
- ⇨ intensity: to be assessed with the following classification:

- Mild: an adverse reaction, generally transient, that does not interfere with the patient's normal daily activities.
- Moderate: an adverse reaction that limits the patient's ability to carry out normal daily activities, but does not prevent their performance.
- Severe: an adverse reaction whose unbearable discomfort or pain make carrying out normal daily activities impossible for the patient.

⇨ action taken by the doctor (e.g.: none, dose reduction, permanent discontinuation)

⇨ outcome (e.g.: death, restoration, improvement, sequels, unknown, etc.)

⇨ causality assessment: related, unrelated.

The Investigator should ask the patient "Have you experienced any discomfort since you have been administered the medication?" (or something similar) with the aim to facilitate reporting of potential adverse reactions by the patient.

11.2.2 Adverse Reactions Requiring Immediate Reporting:

Severe adverse reaction: Any adverse reaction that causes death, threatens life, exacts patient hospitalisation or extension of an already existing hospitalisation, brings about disability or significant/persistent disablement, or represents a congenital abnormality of a birth defect. With reporting purposes, all suspected adverse reactions considered significant from a medical viewpoint, even if they do not satisfy the above criteria, as for example those that place the patient at risk or require an intervention in order to prevent any of the above outcomes, should also be considered severe. Likewise, all suspected transmissions of an infectious agent through a drug should be treated as severe with reporting purposes (RD 1344 / 2007).

In accordance with the "Good Pharmacovigilance Practices of medicines for human use for the pharmaceutical industry", published by the Ministry of Health and Consumption, the marketing authorisation holder should: Record and report to the body competent in matters of pharmacovigilance of the autonomic community where the health professional who has reported the case is practising his/her profession, any suspected adverse reactions occurring in Spain. Such reporting should be done immediately, and in any case within 15 calendar days

from receiving the information (RD 1344 / 2007) (article 24.4 of Law 29/2006, dated 26 July).

11.2.3 Procedures for Severe Adverse Reaction Reporting

If a severe adverse reaction occurred, in addition to recording it in the Case Report Form (CRF) the Investigator should make it known by the sponsoring laboratory within a maximum 24 hours via FAX (or else by telephone), using the specific form enclosed in the CRF (see annex).

In this case he/she should contact:

PPD

PPD

Ipsen Pharma S.A

Tel. PPD

Fax. PPD

The form should be completed with all available information, but in any case the essential information to be stated includes:

- Name, address, contact telephone and profession of the person who reports
- Patient identification with initials or reference code, date of birth (or age), and sex
- Suspected drug
- Suspected reaction

The laboratory sponsoring the study will be in charge of reporting the severe reaction to the Health Authorities (Spanish Medicament Agency [SMA] and

Pharmacovigilance office in the autonomic community where the adverse reaction occurred) within the aforesaid legally established terms.

11.3. Follow-Up and Final Reports

The sponsor will inform the competent bodies of the autonomic communities and the SMA the effective day of study initiation, and they will send a yearly (or more frequent if so requested) follow-up report.

The sponsor will immediately report to the competent bodies of the autonomic communities and to the SMA any substantial incidences (significant protocol modifications, study discontinuation, etc.) that could happen during the conduct of the study.

From three to six months following study completion, the sponsor will send a study final report to the competent bodies of the autonomic communities and to the SMA.

11.4. Publication of Results

The sponsor, together with the co-ordinating investigator, undertakes to publish the study results, be they positive or negative, and such publication will be devoid of any promotional intention.

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PROTOCOL ACCEPTANCE

Co-ordinating Investigator:

I have read the ANAMET study protocol (IPS-TRI-08-01), and I am agreeable to its contents. I am aware of my responsibilities as the study co-ordinating investigator in accordance with the GCP and with Circular Letter 15/2002 that regulates this type of studies.

NAME: PPD

POSITION: CO-ORDINATING INVESTIGATOR

SIGNATURE: _____

DATE: _____

VENUE: H. Vall d'Hebron
Passeig de la Vall d'Hebron 119-129
08035 Barcelona

On behalf of the Sponsor:

NAME: PPD

POSITION: MEDICAL DIRECTOR

SIGNATURE: _____

DATE: _____

VENUE: IPSEN PHARMA S.A.
CTRA. LAUREÀ MIRÓ 395
08980 SANT FELIU DE LLOBREGAT

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