REPORTING AND ANALYSIS PLAN

A MULTICENTRIC, MULTINATIONAL (CHINA AND RUSSIA), RANDOMISED, OPEN, CONTROLLED STUDY OF IMMEDIATE 9 MONTHS ADJUVANT HORMONE THERAPY WITH TRIPTORELIN 11.25 MG VERSUS ACTIVE SURVEILLANCE AFTER RADICAL PROSTATECTOMY IN HIGH RISK PROSTATE CANCER PATIENTS.

PROTOCOL VERSION AND DATE: FINAL 3.0 - 7 JUNE 2013

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Further to your review and agreement to the Reporting and Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

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IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Reporting and Analysis Plan version became the Final Reporting and Analysis Plan

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event/Experience
BR	Biochemical Relapse
BRFS	Biochemical Relapse-Free Survival
CI	Confidence Interval
CRO	Contract Research Organisation
CCI	[redacted]
ECOG	Eastern Cooperative Oncology Group
EFS	Event-Free Survival
FACT-P	Functional Assessment of Cancer Therapy - Prostate
HRQoL	Health-Related Quality of Life
ITT	Intention to Treat
LHRH	Luteinising Hormone-Releasing Hormone
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
OS	Overall Survival
PP	Per Protocol
PSA	Prostate Specific Antigen
PSADT	PSA Doubling Time
CCI	[redacted]
RAP	Reporting and Analysis Plan
CCI	[redacted]
RP	Radical Prostatectomy
SAE	Serious Adverse Event/Experience
SD	Standard Deviation
SF-36	36-Item Short Form Health Survey
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
CCI	[redacted]
US	Ultrasound
WHO	World Health Organisation

1. INFORMATION TAKEN FROM THE PROTOCOL

1.1. Study objectives

1.1.1. Primary objective

To assess the benefit of immediate adjuvant chemical castration after radical prostatectomy (RP) in patients with high-risk prostate cancer expressed as biochemical relapse-free survival (BRFS).

1.1.2. Secondary objectives

To compare the two groups in terms of:

- Event-Free Survival (EFS), Overall Survival (OS), Disease Specific-mortality rate and prostate specific antigen doubling time (PSADT)
- Impact on health-related quality of life (HRQoL)

To assess overall safety of immediate chemical castration.

1.1.3. Ancillary Exploratory objectives

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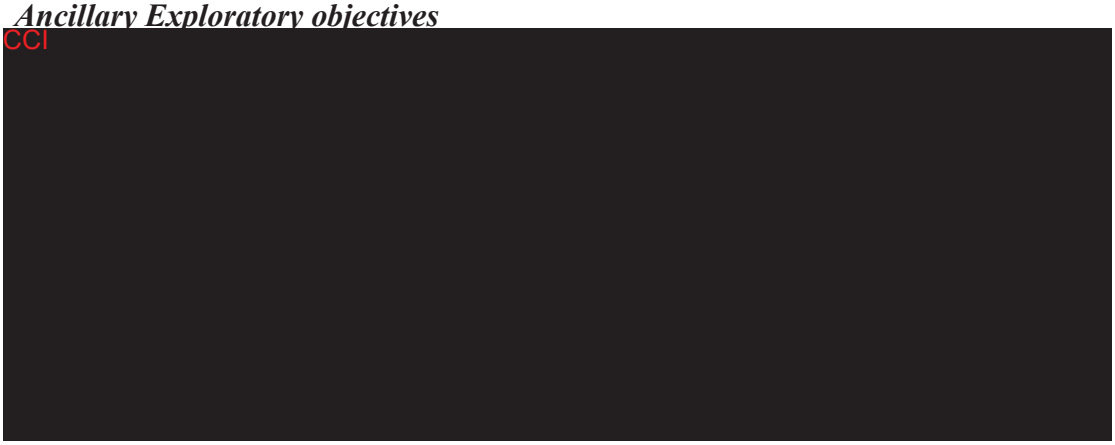

1.2. Study design

This open, prospective, multicentric, multinational, randomised, controlled study with two parallel groups is designed to compare the efficacy and safety of immediate 9-month adjuvant treatment using triptorelin 11.25 mg (treatment onset no later than 8 weeks after RP) versus active surveillance, after RP. Both groups will be monitored at the same frequency of visits (one visit every 3 months). Assessments will be performed to identify any BR/Clinical Disease Progression. This study will be conducted in a Phase IV setting in Russia and China, where triptorelin is approved for the treatment of locally advanced or metastatic prostate cancer.

1.2.1. Study population

The study will be performed in males aged at least 18 years, with histo-pathologically confirmed adenocarcinoma of the prostate, without positive margins, no pathological positive lymph nodes or metastases and with a high risk of disease progression (Gleason score ≥8 on prostatectomy specimen and/or pre-RP PSA level ≥20 ng/mL and/or pT3a). Patients must have undergone RP no more than 8 weeks prior to randomisation, with post-RP (6 weeks) PSA levels ≤0.2 ng/mL, however no other treatment for prostate cancer was permitted. A total of 226 patients will be included from approximately 10 centres, 113 in each group.

1.2.1.1. Inclusion criteria

Each patient must meet the following criteria:

- Provide written informed consent by the patient prior to any study-related procedure
- Men aged ≥18 years
- Histo-pathologically confirmed adenocarcinoma of the prostate
- Radical Prostatectomy with curative intent performed no more than 8 weeks before randomisation
- High-risk criteria of disease progression, defined as follows:
  - Gleason score ≥8 on prostatectomy specimen, and/or
  - Pre-RP PSA level ≥20 ng/mL, and/or
  - Primary tumour stage 3a (pT3a) (with any PSA and any Gleason score)
- Post-RP PSA levels ≤0.2 ng/mL at 6 weeks.
- Eastern cooperative oncology group (ECOG)/world health organisation (WHO) performance status of 0 to 1

1.2.1.2. Exclusion criteria

Patients presenting any of the following criteria were not included in the study:

- Has evidence of lymph nodes or distant metastasis
- Has positive margins
- Has evidence of any other malignant disease, not treated with a curative intent
- Previously received or is currently receiving any treatment of prostatic cancer besides the concerned RP
- Had a surgical castration
- Has a life expectancy of <5 years
- Suffers from a significant comorbidity or an untreated infection
- Is likely to require treatment during the study with drugs that are not permitted by the study protocol
- Has a history of hypersensitivity to triptorelin or any luteinising hormone releasing hormone (LHRH) analogues or to any of the excipients of triptorelin 11.25 mg
- Was treated with any investigational drug within 4 weeks before the study entry

- Has abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the patient's safety or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study
- Is unable to undergo regular follow-up
- Has any mental condition rendering him unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude
- Has a history of, or known current, problems with alcohol or drug abuse.

1.2.2. Study exposure

The anticipated recruitment period of this study is 2 years.

For each patient, study participation is planned to be at least 36 months. Follow-up may continue beyond this if BR is not reported at 36 months and the statistically required 61 BRs have not yet been reached, in which case the patient will continue on study until one of these events occurs.

The overall duration of study is estimated to be approximately 60 months.

1.3. Methods and procedures

1.3.1. Patient identification and allocation to study treatment

All patients enrolled must be identifiable throughout the study. At Screening, potential patients will be allocated a patient number. Patients will be enrolled sequentially and assigned the lowest identification number available.

After eligibility is confirmed, patients will be assigned a randomisation number and will be randomised in one of two treatment arms ("Triptorelin treatment" or "Active surveillance") in accordance with the randomisation procedure.

For patients randomised to the triptorelin treatment group, triptorelin 11.25 mg will be administered intramuscularly every 3 months (±7 days), for a total of three injections (at the Baseline, 3 and 6 months visits). For patients randomised to the active surveillance group, no adjuvant treatment with any method (hormonal or surgical castration and/or radiation therapy) should be initiated prior to evidence of disease progression (clinical or biochemical).

1.3.2. Patients assessments

Methods for derivation of calculated variables are detailed in Section 3.2.10.

1.3.2.1. Efficacy assessments

PSA

Blood samples for PSA testing will be taken every 3 months (except at Visit 2 (Baseline, Day 1 Month 0) where PSA level is not required).

Biochemical Relapse

Biochemical Relapse definition: increased PSA >0.2 ng/mL confirmed by a second measurement performed 4 to 6 weeks later. The time-point at which the first elevated PSA measurement is >0.2 ng/mL is recorded will be deemed to be the time of BR.

To note, for the identification of BR; all PSA samples will be taken into account, even if several samples are within the same time windows.

Clinical disease progression

Clinical disease progression is defined as evidence of local/locoregional recurrence and/or lymph node involvement and/or distant metastases documented by relevant standard investigations (such as ultrasound (US) guided biopsy, X-ray, computed tomography (CT) scan, or magnetic resonance imaging (MRI) guided biopsy).

Survival status

Survival status will be recorded at each visit.

Serum Testosterone

Serum testosterone in the triptorelin treatment group will be recorded at baseline, 3, 6 and 9 months. It will be assessed both as a continuous and as a qualitative variable (< 50 ng/dL / ≥ 50 ng/dL).

Health-Related Quality of Life

Health-Related Quality of Life (HRQoL) will be assessed using the FACT-P questionnaire, version 4, and the 36-item short form (SF-36) health survey, version 2 in both treatment arms at Baseline, 9, 24, and 36 months..

1.3.2.2. Safety assessments

- AE(s) and SAE(s) according to the NCI-CTCAE version 4.0 scale
- Clinical laboratory tests (haematology (full blood count including red blood cells (RBC), haemoglobin, haematocrit, mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), white blood cells (WBC) with differential and platelet count; neutrophils, lymphocytes, monocytes, eosinophils, basophils) and biochemistry (urea, creatinine, total bilirubin, chloride, bicarbonate, sodium, potassium, calcium, inorganic phosphate, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glumatyl transferase (GGT), albumin, total protein, total cholesterol, triglycerides, and fasting glucose)).
- Concomitant medications/therapies and non-drug therapies.
- Concomitant and surgical procedures
- Death reports

- Physical examination and vital signs (height, weight, heart rate and sitting blood pressure (systolic and diastolic).

1.3.2.3. Other assessments

The other assessments will be the following:

- Demography and characteristics at screening:
  - Country,
  - Race (Asian; Black/African American; Caucasian/White; Native Hawaiian/Other Pacific Islander, American Indian/Alaska Native, Multiple),
  - Date of visit,
  - Date of birth.

- Prostate Cancer History (prior to RP)
  - Date of first histological diagnosis
  - Gleason Score (Primary Pattern, Secondary Pattern, Total Score),
  - cTNM Staging (T, N, M) and method used (MRI, CT Scan, X-Ray, Transrectal Ultrasound, Clinical Judgment, Other),
  - Last available PSA level (ng/mL),
  - Last available testosterone level (ng/dL).

- Radical Prostatectomy Procedure
  - Date of surgery
  - Pelvic lymphadenectomy (Yes; No),
  - If yes, extended / not extended,
  - Gleason Score (Primary Pattern, Secondary Pattern, Total Score),
  - pTNM Staging (T, N, M).

- WHO/ECOG Performance Status Scale.

- Significant Medical or Surgical history (including ongoing medical history other than prostate cancer related).

- Prior and concomitant medications/therapies and non-drug therapies.

1.3.2.4. Withdrawal / discontinuation from the study

The date of early withdrawal and the primary reason for early withdrawal will be recorded (adverse event, protocol violation, consent withdrawn, lost-to follow-up, other).

1.3.2.5. Compliance

Compliance assessments will be the following:

- Injection triptorelin administration performed (Yes/No),

- Date of drug administration,
- Date of surgery (radical prostatectomy),
- Dose :
    - Planned volume administered (Yes/No),
    - If no, reason and volume administered (ml).

1.3.3. Schedule of assessments

Table 1. Schedule of Assessments

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	XX
	Screening	Baseline	3M	6M	9M	12M	15M	18M	21M	24M	27M	30M	33M	36M	Every 3M
Informed Consent	X														
Demographic Data	X														
Medical History	X														
Eligibility Criteria	X	X													
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs		X													
ECOG/WHO Performance Status		X			X					X				X	
Randomisation		X													
Testosterone Level [a], [b]		X	X [c]	X[d]	X[d]										
Blood Chemistry and Haematology	X				X										
PSA Level [e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Disease Progression Assessment [f]			X	X	X	X	X	X	X	X	X	X	X	X	X
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Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	XX
FACT-P Questionnaire		X			X					X				X	
SF-36 Health Survey		X			X					X				X	
Triptorelin Injection [a]		X	X	X											
Prior and Concomitant Medication/Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Non-Drug Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs [1]	X	X	X	X	X	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]
Visit Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE, adverse event; CCI ECOG, Eastern Cooperative Oncology Group; FACT P, functional assessment of cancer therapy prostate; M, month; PSA, prostate specific antigen;
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a Only for the triptorelin adjuvant treatment group (± 7 days)

b Always prior to each triptorelin injection (Baseline, 3 months, and 6 months)

c Evidence of lack of castration at 3 months/Visit 3 will be documented by serum testosterone ≥50 ng/dL (≥0.50 ng/mL) confirmed by a second elevated serum testosterone level at least two weeks later. For the other testosterone assessment time points (Baseline, and 6 and 9 months), no confirmation test is required.

d If evidence of lack of castration at 3 months/Visit 3, therefore testosterone sampling is not required anymore at Visit 4/Month 6 and Visit 5/Month 9.

e Starting from Visit 3, any elevated PSA concentration >0.2 ng/mL should be confirmed by a second measurement performed 4 to 6 weeks later. No confirmation test is required after evidence of disease progression (biochemical relapse (BR) and/or clinical disease progression).

f Clinical disease progression assessments (such as ultrasound [US] guided-biopsy, X-ray, computed tomography [CT] scan, magnetic resonance imaging [MRI]) can be performed at any time during the study at the Investigator's discretion and as per local standard care.

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[redacted]

l Adverse events (AEs) will only be collected until Visit 5/Month 9; this corresponds to three months after the last triptorelin injection for those patients in the triptorelin group. After this visit, only AEs and SAEs related to triptorelin according to Investigator's judgement should be reported (with the exception of AEs resulting in death that should be reported until the end of the study).

Patients will not be withdrawn from the study if study medication is discontinued. Follow-up will continue for all patients every 3 months and for at least 36 months.

1.3.4. Planned sample size

It is planned to recruit 226 patients in approximately 10 centres in two countries (China and Russia) according to the Sample Size Determination.

The sample size estimation was based on the primary efficacy endpoint of BRFS. Assuming that with RP alone, the probability of biochemical (PSA) relapse as defined in Section 4.2.1 of the study protocol at 36 months after RP is 40% in high-risk patients (Section 2.1 of the study protocol, Table 1), and anticipating that immediate adjuvant hormonal therapy added to RP will reduce this probability to 20% (percentage considered to be clinically relevant), 113 patients per treatment group (226 in total) are required in order to detect such a difference using a two-sided log-rank test at a significance level of 5% and a power of 90%, assuming a common 1% exponential dropout rate (corresponding to an approximate 5% dropout rate per year).

These 226 patients are required to observe 61 BR in order to achieve 90% power. For patients with no sign of disease progression at 36 months post-randomisation, monitoring will continue until the 61 BR events are observed at the study global level. If the 61 events are observed before all patients complete the 36 months post-randomisation monitoring period, the study will be continued until those patients reach their 36 month visit (Visit 14).

2. PATIENT POPULATIONS (ANALYSIS SETS)

2.1. Screened population

The screened population is defined as all patients with Visit 1 (Screening, Day - 14) performed and who have given informed consent.

2.2. Enrolled population

The enrolled population is defined as all patients from the screened population with visit 2 (Baseline, Day 1) performed.

2.3. Randomised population

The randomised population is defined as all patients from enrolled population who were randomised (i.e. with a randomisation number).

2.4. Safety population

The safety population (SS) is defined as all randomised patients that have received at least one injection for patients from the triptorelin arm or that have undergone at least one day of active surveillance for patients from the active surveillance arm (patient that attended at least one visit after Visit 2 (Baseline, Day 1) or with at least one collected safety data). The patients will be analysed according to the treatment received.

2.5. Intention-to-treat population

The Intention-to-treat population (ITT) is defined as all randomised patients analysed according to the group to which they were randomised (i.e. regardless of treatment approach followed).

2.6. Modified ITT population

The Modified ITT (mITT) is defined as all patients in the ITT population excluding those not treated or without any visit after Visit 2 (Baseline, Day 1). The patients will be analysed according to the group to which they were randomised (i.e. regardless of treatment approach followed).

2.7. Per Protocol population

The Per Protocol (PP) population is defined as all patients in the mITT population for whom no major protocol violations/deviations occurred.
Definition of protocol deviations will be managed in a separate document.
The final status of deviations (minor/major) will be finalized during a blind data review meeting.

Listings of patients regarding inclusion in each population (i.e. satisfying the population definition) and associated data will be reviewed by the study team. Data will be excluded from the PP population on a patient basis and not on a visit basis. Reasons for exclusion from PP population will be presented in a summary table.

2.8. Primary populations

Baseline data (medical history, concomitant disease (pre-treatment AEs and ongoing medical history, prior medications and therapies, baseline symptoms etc.)) will be presented by treatment group and overall for the ITT population. Baseline and demographics characteristics will be repeated on the safety population if there is at least 10 % difference between the safety and the ITT population

The analysis based on the primary efficacy endpoints will be performed on ITT, mITT and PP populations. mITT and PP analyses will only be considered as exploratory.
The secondary efficacy endpoints will be analysed on the ITT population.

The analyses of safety data will be performed on the safety population.

3. STATISTICAL METHODS

3.1. Statistical analysis strategy

All statistical analyses will be performed by the biostatistics unit of AIXIAL using the Statistical Analysis System® (SAS®) software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

The statistical analyses will be performed in accordance with International Conference on Harmonisation (ICH) E9 guideline.

3.1.1. Primary efficacy endpoint

BRFS is defined for each patient by the period in months of time from randomisation to time of Biochemical Relapse.

3.1.2. Secondary efficacy endpoint(s)

The secondary efficacy endpoints are:

- EFS (defined for each patient as the period of time (in months) from randomisation to time of first clinical disease progression or death from any cause).

- OS (defined for each patient as the period of time (in months) between randomisation and death from any cause).

- Disease-specific mortality (measured as the time (in months) between randomisation and death related to prostate cancer).

- PSADT (defined as the time (in months) from the first documented PSA increase >0.2 ng/mL to the time of the first value more than twice that of the first increased value).

- PSA level at each visit.

- Serum testosterone in the triptorelin treatment group at baseline, 3, 6 and 9 months.

- HRQoL (assessed using the Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire, version 4, and the 36-item short form (SF-36) health survey, version 2) in both treatment arms at baseline, 9, 24 and 36 months.

3.1.3. Safety endpoint(s)

The safety endpoints are:

- Signs and symptoms, incidence and severity of all AE(s) regardless of relationship to the study drug graded according to the NCI-CTCAE version 4.0 scale including SAEs and treatment discontinuations due to toxicity.
- Clinical laboratory tests
- Concomitant medications and non-drug therapies
- Concomitant and surgical procedures

3.1.4. Multiplicity

No adjustment for multiplicity will be performed.

3.1.5. Significance testing and estimation

All statistical tests will be performed two-sided with a type I error rate set at 5%.

Quantitative variables will be summarised in statistical tables indicating the number of non missing observations (n), the mean and standard deviation (SD), the two-sided 95% confidence interval (CI) of the mean, the median, the quartiles (Q1 and Q3), the minimum and maximum.

Qualitative variables will be summarised in statistical tables indicating the number of non missing observations (n), frequency, percentage of each modality and the two-sided 95% CI associated.

For all parameters, the number of missing values will also be reported in the tables, but they will not be counted for the percentage calculation (qualitative data).

Time to event data will be analysed using Kaplan-Meier method to obtain the estimates of survival median, their associated 95% CI, survival curves for each treatment group and log-rank test p-value will be provided for treatment comparison. The Cox Proportional hazard model will be fitted to compute hazard ratios and the corresponding 95% CI.
All quantitative variables will be analysed with either analysis of variance (ANOVA) or analysis of covariance (ANCOVA) adjusting for baseline when measured. Treatment effect estimates (differences between treatment groups) will be provided with their associated 95% CI.

3.2. Analysis methods

3.2.1. Efficacy

3.2.1.1. Primary efficacy analysis

The primary efficacy analysis will be performed after 61 BR events have been observed and this analysis will be repeated on the number of BR events observed until the end of study.

The primary efficacy analyses of BRFS will be performed on the ITT population (cf. Section 3.2.10 for derived BRFS).
An exploratory analysis will be performed on the mITT and PP population (only on the total number of BR at the end of the study).
BRFS will be provided by treatment group. A log-rank test (two-sided) will be used to compare BRFS time between the two treatment groups. The Kaplan-Meier method will be used to obtain the estimates of median BFRS associated with each treatment. The 95% CI of the median BRFS time will also be provided.

The syntax with SAS using the LIFETEST procedure will be:

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The Cox Proportional hazard model will be fitted to compute hazard ratios and the corresponding 95% CI with treatment group, country (China as reference), nested effect centre(country) (the largest centre as reference) and Gleason score on prostatectomy specimen (in categories: ≤ 6 / = 7 / ≥ 8, with ≤ 6 considered as the reference) as fixed factors.

The syntax with SAS using the TPHREG procedure will be:

CCI

Interactions between treatment group and each covariate (country, centre(country) and Gleason score) will be tested one by one in separate models as follows:

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P-value of covariates effect as well as interactions effect will be provided. Interaction will be considered as suggestive if p-value < 0.20. Suggestive interaction will be kept:

CCI

The validity of the model will be checked as follows:

- *Check of hypothesis of proportional hazards (graphically),*

This check of hypothesis of proportional hazards can be performed using plots the log of negative log of estimated survivor functions versus the log of time.
The syntax with SAS using LIFETEST procedure will be:

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If the curves are parallel then the hypothesis is checked.

Results will be presented in terms of hazard ratios associated with 95% CI and p-value for treatment group and each other fixed factors.

Survival curves for each treatment group will be plotted on the same graph. Median BRFS time for each group and number of events will be provided.

Should there be a suggestive country*treatment interaction or a centre(country)*treatment interaction, BRFS will also be analysed respectively by country/centre in order to describe any possible country/centre effect. Similarly, should there be a suggestive Gleason score*treatment interaction, BRFS will also be analysed by Gleason score categories (≤ 6 / = 7 / ≥ 8, with ≤ 6 considered as the reference) in order to describe treatment effect within each subgroup.

Sensitivity analyses:

If a patient had at least two consecutive missing visits before the BR, a sensitivity analysis will be performed by censoring this patient at the date of the last visit preceding the missing consecutive visits (cf Section 3.2.10 for derived BRFS).

If patients died (whatever the cause) without BR, a sensitivity analysis will be performed by considering the death as an event (cf Section 3.2.10 for derived BRFS).

If lost to follow-up (prior to BR) is ≥ 5 %. Baseline characteristics will be compared between groups of lost to follow-up and the other patients. If the lost to follow-up baseline characteristics differ from those of the other patients (as shown by 95 % CI), a sensitivity analysis will be performed excluding the lost-to follow-up patients.

Sensitivity analyses will be performed on ITT population on the first 61 BR events and repeated on the number of BR events observed until the end of the study if there is a difference of at least 5% of number of events (i.e. ≥65 events). The Log-rank test will be provided as well as the Cox Proportional hazard model. The interactions will be tested only if suggestive interactions were founded in the main analysis.

The primary efficacy analyses are summarised in the table below:

	ITT population		mITT population	PP population
	61 BR events	All BR events	All BR events	All BR events
Main analysis	X(1)	X	X	X
Sensitivity analysis 1 (censoring of patients with missing visits)	X	X(2)		
Sensitivity analysis 2 (death as an event)	X	X(2)		
Sensitivity analysis 3 (excluding lost-to-FUP patients)	X	X(2)		

(1) Primary analysis
(2) Only if the number of BR events observed until the end of the study is different of at least 5% (i.e. ≥65 events)

3.2.1.2. Secondary efficacy analysis

The secondary efficacy analyses will be performed on the ITT population. In these analyses, no interaction will be tested for EFS, OS, disease-specific mortality and PSA doubling time. For serum testosterone, only patients in the triptorelin-treated group will be included in the analysis

3.2.1.2.1. Event-Free Survival

EFS will be provided by treatment group (cf. Section 3.2.10 for derived EFS).
EFS will be compared between groups using the same analysis and strategy used for BRFS.

3.2.1.2.2. Overall Survival

OS will be provided by treatment group (cf. Section 3.2.10 for derived OS).
OS will be compared between groups using the same analysis and strategy used for BRFS.

3.2.1.2.3. Disease-specific mortality

Disease-specific mortality will be provided by treatment group (cf. Section 3.2.10 for derived disease-specific mortality).
Disease-specific mortality will be compared between groups using the same analysis and strategy used for BRFS.

3.2.1.2.4. PSA Doubling Time

PSADT will be provided by treatment group (cf. Section 3.2.10 for derived PSADT).
PSADT will be compared between groups using the same analysis and strategy used for BRFS.

3.2.1.2.5. PSA level

The PSA level (ng/ml) at each visit (except at Visit 2 (Baseline, Day 1 Month 0) where PSA level is not required) will be described using descriptive quantitative statistics.
PSA level will be described both in its continuous format and in categories (≤0.2 ng/ml; >0.2 ng/ml - <4 ng/ml; ≥4 ng/ml - <10 ng/ml; ≥10 ng/ml)

The percentage change from baseline (defined as the screening values) will be also presented.
In addition, a shift table of the change in categories between baseline and each visit will be presented.

At baseline the last test available before first injection of treatment will be used. Otherwise, in case of several samples (with a result) in the same time windows (excluding the confirmation samples), the value of the last sample will be used.

3.2.1.2.6. Serum testosterone

The proportion of castrated (serum testosterone < 50 ng/dL) patients at baseline and 3, 6 and 9 months post-RP will be provided for the triptorelin treatment group. Shift tables between two consecutive visits and between baseline and end of study will be presented of the number and percentage of patients castrated or not.

The serum testosterone level at baseline and at 3, 6 and 9 months post-RP, as well as the serum testosterone level changes from baseline to 3, 6 and 9 months post-RP will be described using descriptive quantitative statistics.
In case of several samples (with a result) in the same time windows, the value of the first sample will be used.

Changes will be analysed using a repeated-measures analysis of covariance using a mixed linear model with patient as a random effect, baseline and visit (Month 3, Month 6 and Month 9) as fixed factors. Correlation structures (auto-regressive (AR(1)), compound symmetry (CS) and unstructured (UN)) will be tested and the best one will be considered for the model (the model with the smaller AIC will be chosen) :

Change = baseline + visit + e
With:

- Baseline and visit as fixed effects,
- e: error ~ N (0, σe^2).

The syntax with SAS using the MIXED procedure will be:

CCI

[redacted]

3.2.1.2.7. Health-Related Quality of Life

The HRQoL measurements (FACT-P and SF-36v2) are defined as follows:

FACT-P measurements	SF-36v2 measurements

• Subscales:
  ○ Physical well-being
  ○ Social well-being
  ○ Emotional well-being
  ○ Functional well-being
• Dimensions:
  ○ General well-being
  ○ Prostate-specific concerns
• Total FACT-P score
	• Health Domain Scales:
	  ○ Physical functioning (Raw)
	  ○ Role-Physical (Raw)
	  ○ Bodily Pain (Raw)
	  ○ General Health (Raw)
	  ○ Social Functioning (Raw)
	  ○ Mental Health (Raw)
	  ○ Role-Emotional (Raw)
	  ○ Vitality (Raw)
	  ○ Physical functioning (Norm-based)
	  ○ Role-Physical (Norm-based)
	  ○ Bodily Pain (Norm-based)
	  ○ General Health (Norm-based)
	  ○ Social Functioning (Norm-based)
	  ○ Mental Health (Norm-based)
	  ○ Role-Emotional (Norm-based)
	  ○ Vitality (Norm-based)
	• Component Summary measures calculated from a combination of norm-based scales scores:
	  ○ Physical Component Summary
	  ○ Mental Component Summary

These HRQoL measurements at baseline and at 9, 24 and 36 months post-RP, will be described using descriptive quantitative statistics for each treatment group (cf. Section 3.2.10 for derived FACT-P and SF-36v2). In addition the change from baseline will also be presented for each of these HRQoL measurements.

For each HRQoL measurement (subscales, dimensions, scales, component summary measures), changes will be analysed using a repeated-measures analysis of covariance using a mixed linear model with patient as a random effect, baseline, group, visit (Month 9, Month 24 and Month 36) and the interaction between group and visit as fixed effects. Correlation structures (auto-regressive (AR(1)), compound symmetry (CS) and unstructured (UN)) will be tested and the best one will be considered for the model (the model with the smaller AIC will be chosen):

Change = baseline + group + visit + group*visit + e
With:

- baseline, group, visit and group*visit as fixed effects,
- e: error ~ N (0, σe^2).

The syntax with SAS using the MIXED procedure will be:

CCI

3.2.1.3. Exploratory efficacy analysis

To identify prognostic factors among Gleason score on prostatectomy specimen (≤ 6 / = 7 / ≥ 8, with ≤ 6 considered as the reference), country, Pre-RP PSA level (<20 / ≥20 ng/mL), primary tumour stage (T1 / T2 / T3 / T4 with T3 considered as the reference) and age (<65 years / ≥65 years) are associated with BRFS outcome, Cox proportional hazard regression models will be used. Each parameter will be analysed in an univariate model where the hypothesis of proportional risks will be checked graphically. Significant parameters at a 20%-level will be retained for the multivariate Cox model. Associations between significant parameters will be tested in order to keep only non correlated variables in the multivariate model. The association between two categorical or binary variables will be tested using Chi-square or Fisher's exact test. Associations will be considered as statistically significant if p<0.01. A backward selection method will be used to identify the final set of prognostic factors (exit p-value set to be 0.05). Treatment will then be added to this final model to assess the effect of treatment when adjusted for these factors.

The syntax with SAS using the PHREG procedure will be:

CCI

3.2.2. Safety

Safety analysis will be analysed on safety population according to the actual treatment approach followed.

3.2.2.1. Adverse events

Adverse events will be graded by the investigator according to the NCI CTCAE version 4.0.
AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA; version 16.0) and will be classified by PT and SOC.

Listings will be presented for all patients (description, time to onset, duration, seriousness, grade, relationship to study drug, action taken and outcome) and sorted by treatment group, patient id, start time of AEs, primary system organ class, preferred term and verbatim text for all adverse events recorded during the study.

Listings of serious adverse events (SAE), adverse events leading to study withdrawal, leading to study drug discontinuation, drug related adverse events, adverse events with NCI CTC Grade > 2 and listings of deaths will also be presented.
Treatment Emergent Adverse Events (TEAE) will be flagged (*) in the adverse events listing and will be summarised.

For the triptorelin treatment group, a TEAE is defined as any AE that occurs during the active phase of the study if:

- it occurred up to 12 months after the first injection,

and

- it was not present prior to receiving the first dose of study drug, or
- it was present prior to receiving the first dose of study drug but the intensity increased during the active phase of the study, or
- it was present prior to receiving the first dose of study drug, the intensity is the same but the drug relationship became related during the active phase of the study.

Summary tables of adverse events will be provided with the number and percentage of patients with adverse events classified by primary system organ class, preferred term (ordered alphabetically) and associated NCI/CTC worst grade. In the event of multiple occurrences of the same adverse events being reported by the same patient, the maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) and the most serious causality (related) will be chosen.

A summary table of all adverse events will be presented by treatment arm up to visit 6. An overall summary table of all adverse events will be presented starting at visit 6.

For the first year (visit 6 excluded), summary tables of adverse events will be presented separately for each treatment arm:

- For the triptorelin treatment group, treatment emergent adverse events per decreasing frequency, treatment emergent serious adverse events, treatment emergent non serious adverse events, treatment emergent drug related adverse events, treatment emergent drug related serious adverse events, treatment emergent drug related non serious adverse events, treatment emergent adverse events leading to study withdrawal and treatment emergent adverse events leading to study drug discontinuation (drug withdrawn or drug interrupted).

- For the active surveillance group, adverse events per decreasing frequency, serious adverse events, non serious adverse events and adverse events leading to study withdrawal will be presented.

For AEs starting from visit 6, the summary tables of adverse events will be presented overall. The following summary tables will be presented: adverse events per decreasing frequency, serious adverse events, non serious adverse events and adverse events leading to study withdrawal.

3.2.2.2. Laboratory data

A separate listing of normal ranges for SI units will be provided by age where relevant.
Laboratory data (haematology, biochemistry) will be listed in SI units and abnormal values will be flagged (High [H], Low [L], clinically significant [C], NCI-CTC grade (G)) where applicable. Any unscheduled laboratory assessments will be flagged [U] in the listings.
For haematology and biochemistry parameters the baseline will be defined as the screening values.
Summary statistics (mean, median, SD and range as appropriate) by treatment group and overall will be presented for clinical laboratory tests at each assessment (screening and 9 month) with change from baseline.
Shift tables will be presented of the number and percentage of patients with below, within or above normal range. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented.

In case of available retest sample, values of retest sample will be used instead of the first sample, except at baseline where the last test available before first injection of treatment will be used.

3.2.2.3. Vital signs

Descriptive summary statistics will be provided on safety population according to the actual treatment approach followed for vital signs. It includes assessments as detailed in the Section 1.3.2.3 'Vital signs'.

3.2.3. Missing data and outliers

3.2.3.1. Missing data

Missing data will not be imputed and dropouts will not be replaced.
Rules for missing data imputation for HRQoL will be addressed in 3.2.10 Derived Data.

3.2.3.2. Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- The most conservative approach will be systematically considered (i.e. if the onset date concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase except if the partial onset date or other data [stop date, …] indicates differently).
- A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before the study inclusion.
- If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (i.e.: a medication with partial start and stop dates could be considered as prior and concomitant treatment).
- Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e. for a medication started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing medication will be"≥xx" according to the start and last visit dates).

3.2.3.3. Outliers

Any outlier identified prior to data base lock which is impossible/implausible will be excluded from the analysis.
For other identified outliers, the impact should be assessed by performing the statistical analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect.
If any outliers are identified after the database lock, the statistical analysis should be performed with the actual values and at least one other analysis eliminating or reducing the outlier effect.
A search of outliers for the PSA result will be performed before the database lock and actions with the sponsor will be defined during data review meeting.

3.2.4. Patient disposition

A summary table will present the number and percentages of patients enrolled included in each analysis set by treatment group and overall, by country and centre.
The reason for patients' exclusion from each of the analysis set will also be tabulated.

The numbers of patients who were randomised, discontinued and completed the study will be tabulated by treatment group and overall. A patient is considered as having completed the study when "Completed the study" is ticked in the CRF at visit 14 (Month 36) or at one of the follow-up visit. The primary reason for early withdrawal will be provided (adverse event, protocol violation, consent withdrawn, lost-to follow-up, other) by treatment group and overall.

A summary table (and a flow chart) will be performed for each analysis set (Safety population, ITT and PP population) presenting the number and proportion of patients by treatment group and overall at each visit.

A summary table will present the duration of study drug exposure and the extent of patient exposure in the study (months). The length of exposure is defined as the number of days between the date of consent and the last study visit date.
A listing of dates of visit and calculated time interval since baseline visit (days) will be presented by patient.

3.2.5. Withdrawals from study

Discontinued patients will be listed and a summary table of the number and percentage of patients who withdrew from the study and the reasons for withdrawal will be presented overall and by treatment group.

3.2.6. Demographic and baseline characteristics

Descriptive summary statistics will be provided by treatment group and overall on the ITT population and on the safety population if there is at least 10 % difference between the safety and the ITT population, for demographic and baseline characteristics. It includes assessments as detailed in the Section 1.3.2.3 ('Demography and characteristics at baseline', 'Prostate cancer history', 'Radical prostatectomy procedure' and 'WHO/ECOG Performance Status Scale'). To assess homogeneity of treatment groups at baseline, 95% CI of proportion for qualitative variable or 95% CI of mean for quantitative variable will be provided.
In addition the proportion of patients with a Gleason score ≥8 on prostatectomy specimen and with a Pre-RP PSA level ≥ 20 ng/mL; with a Gleason score ≥8 on prostatectomy specimen and with a primary tumour stage 3a; with a Pre-RP PSA level ≥ 20 ng/mL and with a primary tumour stage 3a; with a Gleason score ≥8 on prostatectomy specimen and with a Pre-RP PSA level ≥ 20 ng/mL and with a primary tumour stage 3a will be tabulated.

3.2.7. Medical and surgical history

Descriptive summary statistics will be provided by treatment group and overall on the ITT population for 'Significant Medical or Surgical History'.

A frequency table of the number and percentage of patients will be provided for medical history by SOC and PT.

3.2.8. Compliance

Descriptive summary statistics will be provided by treatment group and overall on the ITT population, for current prostate cancer therapy. It includes assessments as detailed in the Section 1.3.2.5 'Compliance' and the time between first drug administration and RP (days) and the time between each drug intake (days). .

If the drug intake occurs outside the allowed time-window (time between each drug intake should be between 84 and 99 days (3*30.4375 ± 7 days)), the date of dose intake and the number of days since the last drug intake will be listed.

3.2.9. Prior and concomitant medications and non-drug therapies

Descriptive summary statistics will be provided by treatment group and overall on the safety population for 'Prior and concomitant medications and non-drug therapies'.

Prior and concomitant medications:

Prior and concomitant medications will be coded using WHO-Drug Dictionnary March 2013 version. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code.

Listings containing prior and concomitant medications will be presented for the therapeutic class, preferred name and verbatim text, and will be sorted by country, centre, patient, chronological start date, therapeutic class, preferred name and verbatim text.

A frequency table of the number and percentage of patients will be provided for prior and concomitant medications only by therapeutic class and preferred name.

Prior and concomitant non-drug therapies and surgical procedures:

Prior and concomitant non-drug therapies will be coded using MedDRA version 16.0 and will be classified by Preferred Term (PT) and System Organ Class (SOC).

A concomitant therapy will be defined as a therapy started prior to baseline visit date and ongoing at baseline visit date, or started the day of baseline visit or after.

Listings containing prior and concomitant non-drug therapies will be presented for the SOC, PT and verbatim text, and will be sorted by country, centre, patient, chronological start date, SOC, PT and verbatim text.

A frequency table of the number and percentage of patients will be provided for prior and concomitant non-drug therapies only by SOC and PT.

An individual data listing containing concomitant surgical procedures will also be provided.

3.2.10. Derived data

The derived data are variables which are calculated from the raw data and not included in the database.

Age

Patient age (years) will be derived as (baseline visit date – birth date)/365.25 and truncated to the largest integer that is less than or equal to the calculated result.

Time since the first histological diagnosis

Time since the first histological diagnosis (months) will be derived as
(Date of screening visit – Date of first histological diagnosis +1)/ 30.4375 and truncated to the largest integer that is less than or equal to the calculated result.

Partial dates of histological diagnosis will be imputed to calculate times:

- If the day is missing and month is present, the 15 of the month will be used.
- If the day and month are missing, the 15 of June will be used.

Radical Prostatectomy Procedure

Time between screening visit and surgery (weeks) will be derived as (Screening Visit Date - Date of radical prostatectomy+1) / 7.

Compliance

Time between first drug administration and RP (weeks) will be derived as (Date of first drug administration - Date of radical prostatectomy+1) / 7.

Time between each drug intake (weeks) will be derived as (Date of drug intake at Visit t – Date of drug intake at visit $_{t-1}$ +1) / 7.

Partial dates of treatment will be imputed to calculate times:

- If the day is missing and month is present the 15 of the month will be used.
- If year is present and day and month are missing then the difference between years will be used.

Changes from baseline
Changes from baseline will be calculated as a difference from baseline (e.g. assessment at the visit – assessment at baseline).

Length of patient exposure in the study
Length of patient exposure in the study (months) will be calculated as [(Date of last visit attended – informed consent date) +1] / 30.4375.

Duration of study drug exposure
Duration of study drug exposure (months) will be calculated as [(Date of last drug administration – Date of first drug administration) / 30.4375] + 3.

Adverse event
Time to onset of AE (days) = AE start date – date of randomisation.

Duration of AE (days) = (AE resolution date – AE start date) + 1.

Time-to-event criteria
BRFS (months) will be derived as (Date of first BR – date of randomisation + 1) / 30.4375.

EFS (months) will be derived as (Date of clinical disease progression or death from any cause – date of randomisation + 1) / 30.4375.

OS (months) will be derived as (Date of death from any cause – date of randomisation + 1) / 30.4375.

Disease specific mortality will be derived as (Date of death related to prostate cancer – date of randomisation + 1) / 30.4375.

PSADT (months) will be derived as (Date of sample when the first PSA value > than twice that of the first increased value – Date of sample of the first PSA value increased value (i.e. > 0.2 ng/mL) + 1) / 30.4375.

All of these time-to-event variables will be rounded to 1 decimal.
For BRFS, EFS, OS and Disease specific mortality, if the date of event or censor is prior to the date of randomisation, the data of event or censor taken into account will be the date of randomisation.

Rules for time-to-event data

The following table defines the rules for censoring data (for Kaplan-Meier analysis)

- BRFS

Event	Decision	Date of event or censor to consider for analysis
BR	Not censored	Date of BR (i.e. date of the first elevated PSA measurement is >0.2 ng/mL*)
No BR and no clinical disease progression and new hormonal treatment (ie triptorelin or similar)	Censored	Date of last evaluable sample before the start of new hormonal treatment
No BR and no clinical disease progression and no premature withdrawal from the study	Censored	Date of last evaluable sample assessment
No BR and no clinical disease progression and patient premature withdrawal from the study or lost to follow-up	Censored	Date of last evaluable sample before withdrawal from the study or last contact
Clinical disease progression before BR	Censored	Date of clinical disease progression
No BR but death	Censored	Date of last evaluable sample assessment

- BRFS – Sensitivity Analysis 1

Event	Decision	Date of event or censor to consider for analysis
BR	Not censored	Date of BR (i.e. date of the first elevated PSA measurement is >0.2 ng/mL*)
At least two consecutive visits missing before BR	Censored	Date of last visit preceding the missing consecutive visits
No BR and no clinical disease progression and new hormonal treatment (ie triptorelin or similar)	Censored	Date of last evaluable sample before the start of new hormonal treatment
No BR and no clinical disease progression and no premature withdrawal from the study	Censored	Date of last evaluable sample assessment
No BR and no clinical disease progression and patient premature withdrawal from the study or lost to follow-up	Censored	Date of last evaluable sample before withdrawal from the study or last contact
Clinical disease progression before BR	Censored	Date of clinical disease progression
No BR but death	Censored	Date of last evaluable sample assessment

- BRFS – Sensitivity 2

Event	Decision	Date of event or censor to consider for analysis
BR	Not censored	Date of BR (i.e. date of the first elevated PSA measurement is >0.2 ng/mL*)
Death (whatever the reason) without BR	Not censored	Date of death
No BR and no clinical disease progression and new hormonal treatment (ie triptorelin or similar)	Censored	Date of last evaluable sample before the start of new hormonal treatment
No BR and no clinical disease progression and no premature withdrawal from the study	Censored	Date of last evaluable sample assessment
No BR and no clinical disease progression and patient premature withdrawal from the study or lost to follow-up	Censored	Date of last evaluable sample before withdrawal from the study or last contact
Clinical disease progression before BR	Censored	Date of clinical disease progression

- EFS

Event	Decision	Date of event or censor to consider for analysis
Clinical disease progression or death from any cause	Not censored	Date of clinical disease progression or death
No clinical disease progression and no death and no premature withdrawal from the study	Censored	Date of last visit
No clinical disease progression no death and patient premature withdrawal from the study or lost to follow-up	Censored	Date of withdrawal from the study or last contact

- OS

Event	Decision	Date of event or censor to consider for analysis
Death from any cause	Not censored	Date of death
Patient alive and no premature withdrawal from the study	Censored	Date of last visit
Patient premature withdrawal from the study or lost to follow-up	Censored	Date of withdrawal from the study or last contact

- Disease-specific mortality

Event	Decision	Date of event or censor to consider for analysis
Death related to prostate cancer	Not censored	Date of death
Death not related to prostate cancer	Censored	Date of death
Patient alive and no premature withdrawal from the study	Censored	Date of last visit
Patient premature withdrawal from the study or lost to follow-up	Censored	Date of withdrawal from the study or last contact

- PSADT

Event	Decision	Date of event or censor to consider for analysis
First PSA value > than twice that of the first increased value (> 0.2 ng/mL)	Not censored	Date of sample when the first PSA value > than twice that of the first increased value
No PSA value 2 times higher than the first increased value or no increased value and no premature withdrawal from the study	Censored	Date of last evaluable sample
Patient premature withdrawal from the study or lost to follow-up	Censored	Date of last evaluable sample before withdrawal from the study or last contact

Incomplete dates for time-to-event analyses will be handled as follows:

- If the day of the randomisation is missing and month is present, the 15 of the month will be used.
- If the day of the BR, clinical progression or death is missing and month is present, the 01 of the month will be used.
- If the month (or the date) of the death is missing, the date of the last contact will be used.
- The other dates with missing month will be studied case by case.

Castrated patients

A patient will be considered as:

- Castrated if the testosterone level is inferior to 50 ng/dL for the test or confirmation test.
- Not castrated if the testosterone level is superior or equal to 50 ng/dL for the test and confirmation test.

HRQoL

- FACT-P

The FACT-P score is composed of 27 general questions about physical, social, emotional, and functional well-being as well as a 12-item questionnaire about prostate-specific concerns. A maximum score of 156 points indicates the highest level of QoL. The total FACT-P score will be calculated as the sum of 39 item scores.

Dimensions	Subscales	Number of items	N° item
General well-being	Physical well-being Social well-being Emotional well-being Functional well-being	7 7 6 7	GP1 to GP7 GS1 to GS7 GE1 to GE6 GF1 to GF7
Prostate-specific concerns	--	12	C2, C6 P1 to P8 BL2 to BL5

For missing data, if less than 50 % of the items are missing, subscale scores will be prorated. This will be done by using the formula below:

Prorated subscale score = (Sum of item scores)*(Number of items in the subscale)/ (Number of items answered).

If more than 50 % of the items are missing from any subscale, the subscale will not be imputed.

For any given scale, if the missing values represent more than 10 % of the population; two analyses will be performed. One analysis using the available values and a second analysis imputing the missing values by the mean value of the available data at the concerned timepoint will be performed.

- SF-36v2

The SF-36 health survey version 2 [1] is composed of 36 items about 8 Health Domain Scales: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), Social Functioning (SF), Mental Health (MH), Role-Emotional (RE), Vitality (VT) and General Health (GH).
All but one of the 36 items (item n°2: self-reported health transition) are used to score the eight raw Health Domain Scales. Each item is used in scoring only one scale. The response for each item is recoded according to the table below.
Then, the eight Health Domain Scales Total Raw Scores are calculated, according to the table on the following page. Each score will range from 0 to 100, where 0 represent the lowest possible score (worst health state) and 100 represent the highest possible score (best health state).

Finally, the eight health domain scales scores are normed to the 2009 U.S. general population to have a mean of 50 and a standard deviation of 10. These are health domain scales norm-based scores.

Two summary measures are calculated, using the eight health domain scales norm-based scores and an algorithm: an overall score of physical health (Physical Component Summary or PCS) and overall score of mental health (Mental Component Summary or MCS)

Item numbers	Precoded response value	Final response value
3a to 3j	1 2 3	3 2 1
2 4a to 4d 5a, 5b, 5c 9b, 9c, 9f, 9g, 9i 10, 11a, 11c	1 2 3 4 5	5 4 3 2 1
7	1 2 3 4 5 6	6 5 4 3 2 1
1 6 8 9a, ,9d, 9e, 9h 11b, 11d	1 2 3 4 5	5 4 3 2 1

Component Summary measures (calculated from a combination of norm-based scales scores)	Health Domain Scales (raw and norm-based)	Number of items	Items
Physical Health (PCS)	Physical functioning (PF) Role-Physical (RP) Bodily Pain (BP) General Health (GH)	10 4 2 5	3a to 3j 4a to 4d 7, 8 1, 11a to 11d
Mental Health (MCS)	Social Functioning (SF) Mental Health (MH) Role-Emotional (RE) Vitality (VT)	2 5 3 4	6, 10 9b, 9c, 9d, 9f, 9h 5a, 5b, 5c 9a, 9e, 9g, 9i

The derivations of the eight Health Domain Scales Total Scores (Raw and norm-based) and the two component summary measures (calculated from a combination of norm-based scales scores) will be performed using software application delivered by QualityMetric.

Missing data are ignored and the scale is calculated without the missing item. If more than 50 % of the items are missing from any scale, the scale score will not be calculated.

For any given value, if the missing values represent more than 10 % of the population; two analyses will be performed. One analysis using the available values and a second analysis imputing the missing values by the mean value of the available data at the concerned timepoint will be performed.

3.2.11. Visit windows

All data will be organised and analysed according to the scheduled visits outlined in the protocol. However, actual observation times may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit. Therefore, time intervals (e.g. visit windows) have been constructed so that every observation collected after baseline visit can be allocated to a particular time point. If more than one record occurs within the same visit window where only one assessment is expected then the following rule should be applied (except for PSA and testosterone sample): for pre-study assessments only one record is expected and corresponds to the baseline visit; for post-treatment assessments the closest non-missing result to the scheduled visit should be used.

Scheduled visit	**Time interval (days)**
Baseline [V2]	1
Month 3 [V3]	2 to 138
Month 6 [V4]	139 to 229
Month 9 [V5][(a)]	230 to 321
Month 12 [V6]	322 to 412
Month 15 [V7]	413 to 503
Month 18 [V8]	504 to 595
Month 21 [V9]	596 to 686
Month 24 [V10][(a)]	687 to 777
Month 27 [V11]	778 to 868
Month 30 [V12]	869 to 960
Month 33 [V13]	961 to 1051
Month 36 [V14][(a)]	1052 to 1142
X visit post Month 36 - Every 3 months	((36+3*X-1.5)*30.4375+2) to ((36+3*X+1.5)*30.4375+1)
Time interval (days): Date of visit – Date of baseline visit +1 (a) sHRQoL assessment	

3.2.12. Window for assessment for the PSA and testosterone parameters

Testosterone (only in the triptorelin treatment group) should be assessed at 3; 6 and 9 months (±14 days). At visit 3, evidence of lack of castration will be confirmed by a second test at least 2 weeks later.

PSA should be assessed every 3 month (±14 days) except at Visit 2 (Baseline, Day 1 Month 0). Elevated PSA concentration (>0.2 ng/mL) must be confirmed by a second test 4 to 6 weeks later (acceptable delta of 14 days).

Scheduled visit	Time interval (days) for serum testosterone assessment		Time interval (days) for PSA Level assessment	
	As per protocol (±14 days)	Used for analysis (Consecutive intervals)	As per protocol (±14 days)	Used for analysis (Consecutive intervals)
Month 3 [V3][a,b]	78 to 106	2 to 138	78 to 106	2 to 138
Month 6 [V4][a,b]	170 to 198	139 to 229	170 to 198	139 to 229
Month 9 [V5][a,b]	261 to 289	230 to 321	261 to 289	230 to 321
Month 12 [V6] [b]	--	--	352 to 380	322 to 412
Month 15 [V7] [b]	--	--	444 to 472	413 to 503
Month 18 [V8] [b]	--	--	535 to 563	504 to 595
Month 21 [V9] [b]	--	--	626 to 654	596 to 686
Month 24 [V10][b]	--	--	718 to 746	687 to 777
Month 27 [V11] [b]	--	--	809 to 837	778 to 868
Month 30 [V12] [b]	--	--	900 to 928	869 to 960
Month 33 [V13] [b]	--	--	991 to 1019	961 to 1051
Month 36 [V14][b]	--	--	1083 to 1111	1052 to 1142

Time interval (days): Date of assessment – Date of baseline visit +1
(a) serum testosterone assessment
(b) PSA Level assessment

3.2.13. Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).
For summary statistics, the following will be presented: n, arithmetic mean, standard deviation, median, first quartile, third quartile, minimum and maximum.

Mean, median, quartiles and standard deviation values will be reported to one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data.

Percentages will be reported to one decimal place and 0% will not be presented. Percentages will be calculated using a denominator of all patients in a specified population with non-missing observations. The denominator will be specified in a footnote to the tables for clarification if necessary.

P-values will be reported to three decimal places (e.g.: p=0.037), after rounding. P-values which are less than 0.001 will be presented as '<0.001'.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such. In summaries of data values below limit of detection will be set to the limit of detection. Values above limit of detection will be set to limit of detection.

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified. Dates and times will be presented in the format as defined in the data-base, i.e. [ddmmmyyyy] and [hh:mm] respectively.

3.2.14. Pooling of Centres

It is not planned to perform a subgroup analysis on individual or groups of centres. To compute hazard ratios on the primary endpoint a Cox Proportional hazard model will be fitted including treatment group, Gleason score, country and pooled centres.
In each country, the centres with a randomized number of patients strictly above 10 will be pooled in one centre.

3.2.15. Interim analysis

Primary endpoint analysis will be performed once the 61 BRs are provided. Tables/figures/listings to be produced for this analysis are flagged in the index by a *.

3.2.16. Covariates and analysis of subgroups

If analysis of primary efficacy criterion can highlight a country effect then an adjustment for country will be done for efficacy analyses.

4. COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1. Hardware

The statistical analysis will be performed using Microsoft Windows 7 Enterprise and PCs will be used to run the SAS® programs.

4.2. Software

All tables, listings and figures will be produced and statistical analysis performed using SAS® version 9.4. All output will be in Microsoft Word Format.

4.3. Validation programs

Validation of SAS programs will be performed by Lincoln as described in Lincoln Standard Operating Procedure "Analyse statistique".
The CRO will provide a Validation Plan to Ipsen identifying the methods of validation.
The Program Reviewer is responsible for reviewing each project program and output associated with the deliverable product. Program logs are reviewed for logical, syntax and fatal errors. The review in SAS includes, but is not limited to, all ERRORS, WARNINGS, BY-VALUE merge messages, NOTES, and UNINITIALIZED variables. Program logs are also reviewed for accurate and consistent variable and observation counts following each procedure and data step.
The Reviewing/QC Statistician is responsible for checking and reviewing the work produced using whatever method he/she feels is appropriate (e.g., SAS code review, hand calculation, etc.) to reassure of the quality of the output.
Outputs are reviewed for typographical errors, misspellings and nonsensical values or results and to check the consistency with the reporting and analysis plan. Outputs are cross-checked against each other for accuracy and consistency. For statistical tables, listings, appendix listings, and figures, this procedure includes comparison of patient group numbers, counts of patients at each observation point, and consistency of results for variables between outputs.
Findings of the quality control reviews are communicated to the party responsible for making necessary changes. The programs will be retested after modifications.
After final review, and when no further changes are required to produce the deliverable, the Program Reviewer and Reviewing/QC Statistician need to complete and sign the CRO's Validation Checklist/Sign-off Sheet, to indicate that they have successfully performed all of their responsibilities.

Copies of the internal QC forms produced for the validation process and the Lincoln's sign-off forms will be provided to the sponsor to support the validation.

4.4. Restitution of the programs

All programs (including Macros specifically written for this study and analysis datasets) producing the tables, listings and statistical output along with associated logs should be given to the sponsor when the tables, listings, figures and statistical analysis has been finalised.

5. CHANGES FROM PROTOCOL

The screened population have been defined as all patients with Visit 1 (Screening, Day - 14) performed and who have given informed consent.

The enrolled population have been defined as all patients from the screened population with visit 2 (Baseline, Day 1) performed.

The safety population have been defined as all randomised patients that have received at least one injection for patients from the triptorelin arm or that have undergone at least one day of active surveillance for patients from the active surveillance arm (patient that attended at least one visit after Visit 2 (Baseline, Day 1)) or with at least one collected safety data). The patients will be analysed according to the treatment received.

The mITT population has been added.

For primary endpoint, two other sensitivity analyses have been added:

- Censor the subjects if there are at least two missing consecutive visits before the BR.
- Consider death (whatever the cause) as an event.

The rules to apply if more than one record occurs within the same visit window have been changed for PSA and testosterone samples:

6. REFERENCES

1. Maruish, M. E. (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated

7. DATA PRESENTATION

Data listings are presented for all enrolled and randomised patients.
Footnotes should be used to clarify ambiguities (e.g.: the denominator used to calculate a percentage or for notes for the programmer). If the number of footnotes is high, they could be presented only in the last page, with on each page the following footnote "See last page for listing notes". The order of the footnotes for key symbols (*, ~) will be in the order that they appear in the listing.
The title of each generated table, listing and figure should appear bookmarked within Word (one single bookmark per table/listing/figure) to allow document publishing by Ipsen.