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

STUDY PROTOCOL
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Study Short Title: PRIORITI
[TRIPTORELIN 11.25 mg FORMULATION]

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I have read and agree to the study A-38-52014-194 "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". I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP)[1], local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

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1. ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

SYNOPSIS

Study Title:	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.
Study Objectives:	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). Secondary objectives: • To compare the two arms in terms of: - Event-Free Survival (EFS), Overall Survival (OS), 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 Ancillary Exploratory Objectives: CCI [redacted]
Phase of Trial:	Phase IV
Study Design:	This open, prospective, multicentric, multinational, randomised, controlled study with two parallel arms is designed to compare the efficacy and safety of immediate 9-month adjuvant treatment using triptorelin 11.25 mg versus active surveillance after RP. Immediate adjuvant treatment is defined as a treatment being initiated 8 weeks after RP. Visit 1: Screening visit: Six weeks (± 3 days) after RP, the patient will be proposed participation in the study. After the patient has given his written

	informed consent, he will undergo, among other assessments, a blood sampling for serum post-RP prostate specific antigen (PSA) level. Visit 2: Baseline visit (Randomisation): Two weeks after the screening visit, and no more than 8 weeks (± 3 days) after RP when post-RP PSA level is available, eligible patients will be randomised to one of two arms, either the triptorelin treatment arm or to the active surveillance arm. For patients randomised to the triptorelin treatment arm, 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 month visits). For patients randomised to the active surveillance arm, no adjuvant treatment with any method (hormonal or surgical castration and/or or radiation therapy) should be initiated prior to evidence of disease progression (clinical or biochemical). They will be monitored in the same way as for the triptorelin treatment arm. Visit 3 to Visit 14: Monitoring Period: All randomised patients (in both arms) will be followed every 3 months (± 1 week) to monitor the occurrence of biochemical relapse (BR) and/or clinical disease progression over a period of 36 months after randomisation (from Visit 3 to Visit 14). Disease progression is defined as BR and/or clinical disease progression (whichever occurs first): • BR is defined as the first elevated PSA value >0.2 ng/mL confirmed by a second measurement recorded 4 to 6 weeks later. The time-point at which the first PSA value above 0.2 ng/mL is recorded, will be deemed to be the time of BR. • 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). Any patient (in either arm) who has disease progression at any time will receive appropriate medical care from the Investigator. New/additional therapy (for example radiation therapy, surgical castration, or hormonal treatment) will be proposed according to the Investigator's decision and in line with local standard of care. In both arms and depending on the time of occurrence of disease progression, the patient's visit schedule will be as follows: • If BR and/or clinical disease progression occurs before 36 months, the patient will continue to be monitored until 36 months post-randomisation (Visit 14) at which point he will be considered to

	have completed the study. • If at 36 months (Visit 14), the patient has not shown any sign of BR and/or clinical disease progression, and if the statistically required 61 BRs were not observed at the global study level, he will enter the follow-up period. Post-Visit 14: Follow-up Visits: If at 36 months post-baseline (at Visit 14), the patient does not have BR and/or clinical disease progression and if the statistically required 61 BRs are not observed at the global study level, he will continue to be followed every 3 months until: • He has a BR and/or clinical disease progression • Or, the 61 required BRs are observed on the global study level. PSA levels, physical examinations and clinical disease progression assessments (where deemed necessary by the Investigator and in accordance with local standards of care) will continue to be performed at each follow-up visit to monitor disease progression. The study will be considered to be terminated when: • All included patients have completed their minimum monitoring period of 36 months. • And, when 61 BRs are observed at the global study level. Study Completion/Early Withdrawal Visit: Patients who have disease progression (BR and/or clinical disease progression) within 36 months (event documented before Visit 14) will continue to be monitored until Visit 14 which will be considered as the Study Completion Visit. Patients who have disease progression after 36 months (event documented during or after Visit 14) will be considered to have completed the trial. Their last study visit would be the visit when disease progression is documented. After 36 months, patients who do not have disease progression during the whole study will be considered to have completed the trial once the statistically required 61 BR events occur on the study global level. At any time during the study and for any reason, in the case of early withdrawal/discontinuation, the Investigator should perform a last monitoring/follow-up visit considered as the early withdrawal visit. Study Duration: Estimated recruitment period: 24 months Minimum patient participation duration: 36 months after randomisation (for both arms) Estimated study duration: a minimum of 60 months
Study Population:	Number of expected patients: 113 in each arm (226 in total). Number of sites: approximately 10 sites will participate to the study, in China and Russia.

	Inclusion criteria: All patients must fulfil the following: 1. Provide written informed consent signed by the patient prior to any study-related procedure 2. Men aged ≥18 years 3. Histo-pathologically confirmed adenocarcinoma of the prostate 4. Radical Prostatectomy with curative intent performed no more than 8 weeks before randomisation 5. 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 level and any Gleason score) 6. Post-RP PSA levels ≤0.2 ng/mL at 6 weeks. 7. Eastern cooperative oncology group (ECOG)/world health organisation (WHO) performance status of 0 to 1 Exclusion criteria Patients will not be included in the study if any of the following apply: 1. Has evidence of lymph nodes or distant metastasis 2. Has positive margins 3. Has evidence of any other malignant disease, not treated with a curative intent 4. Previously received or is currently receiving any other treatment of prostatic cancer besides the concerned RP 5. Had surgical castration 6. Has a life expectancy <5 years 7. Suffers from a significant comorbidity or an untreated infection 8. Is likely to require treatment during the study with drugs that are not permitted by the study protocol 9. 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 10. Was treated with any investigational drug within 4 weeks before the study entry 11. 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 12. Is unable to undergo regular follow-up 13. 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

	14. Has a history of, or known current, problems with alcohol or drug abuse
Study Treatment:	Investigational medicinal product (IMP): Triptorelin 11.25 mg Pharmaceutical form: Powder and solvent for suspension for intramuscular injection, prolonged released formulation. Active component: Triptorelin pamoate, as triptorelin 11.25 mg Drug name: • China: Triptorelin pamoate for injection, 15 mg • Russia: Diphereline® 11.25 mg Posology and method of administration: Triptorelin will be administered as a hormonal adjuvant to RP for patients randomised to the triptorelin treatment arm. These patients will receive one intramuscular injection of the product, which will be repeated every 3 months for a total of three injections: at Baseline and at the 3 month and 6 month visits.
Study Evaluations:	**Primary Efficacy Endpoint(s) and Evaluation(s):** Biochemical Relapse-Free Survival (BRFS) is defined for each patient by the period of time from randomisation to time of BR. Biochemical Relapse (BR) 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. BRFS data will be censored on the date of the last assessment on study for patients who do not have BR or on the date of clinical disease progression for those who progress before BR while on study or on the date of death for those who die before BR while on study (of any cause). **Secondary Efficacy Endpoints And Evaluations:** • EFS as defined for each patient as the period of time from randomisation to time of first diagnosed locoregional disease recurrence (positive biopsy and/or node involvement) or first metastases (bone or visceral) documented by relevant standard investigations (US guided biopsy, X-ray, CT scan, or MRI guided biopsy) or death from any cause. • OS defined as the time between randomisation and death from any cause. • Disease-specific mortality measured as the time between randomisation and death related to prostate cancer. • PSADT defined as the time 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.

	• Serum testosterone in the triptorelin arm at Baseline, 3, 6 and 9 months. • HRQoL assessed using the Functional 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. **Exploratory Endpoints and Evaluations:** CCI [redacted] **Safety Endpoints and Evaluations:** Signs and symptoms, incidence and severity of all AEs, regardless of relationship to the study drug, graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0, including serious AEs (SAEs) and treatment discontinuations due to toxicity will be monitored from the time that the patient gives informed consent until Visit 5/Month 9 (3 months after the last injection for those patients in the triptorelin arm). After this period, only AEs/SAEs related to triptorelin will be reported.
Statistical Methods:	This study is designed to demonstrate that RP and immediate adjuvant hormonal therapy can significantly improve BRFS compared with RP alone. Sample size: Assuming that with RP alone, the probability of biochemical (PSA) relapse at 36 months after RP is 40% in high risk patients, and anticipating that immediate adjuvant hormonal therapy added to RP will reduce this probability to 20%, 113 patients per treatment group (226 in total) will be 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 will be required to observe the 61 BRs in order to achieve the 90% power. For those with no sign of disease progression, patient monitoring will continue beyond 36 months post-randomisation as long as the 61 BR events are not observed across all patients. If the 61 BR events are observed before all patients have completed the 36 month monitoring period, the study will be continued until those patients reach their 36 month visit (Visit 14). Populations: Three study populations are defined: • Safety Population: 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. Patients will be analysed as treated for the safety analyses. • Intent-to-Treat (ITT) Population: includes all randomised patients analysed according to the arm to which they were randomised. • Per Protocol Population: all patients in the ITT population for whom no major protocol violations/deviations occurred. Analyses: All efficacy endpoints and patient demographics will be evaluated in the ITT. Treatment administration/compliance and safety will be analysed in the safety population. The primary endpoint is BRFS, which is defined as the time from date of randomisation to BR. BRFS data will be censored on the date of the last assessment on study for patients who do not have BR or on the date of clinical disease progression for those who progress before BR while on study or on the date of death for those who do die before BR while on study (for any cause). The primary analyses of BRFS will be performed in the ITT population. A two-sided log-rank test will be used to compare BRFS time between the two treatment groups with nominal significance level 0.05 (two-sided). The Kaplan-Meier method will be used to obtain the estimates of median event-free time associated with each treatment. The 95% confidence intervals (CI) of the median event-free time will be provided also. The Cox Proportional hazards model will be fitted to compute hazard ratio and the corresponding 95% CI.

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Word Definition
AD	Androgen Deprivation
AE	Adverse Event/Experience
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of co-variance
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
BR	Biochemical Relapse
BRFS	Biochemical Relapse-Free Survival
CA	Competent Authorities
CDDS	Clinical Development Data Sciences (relates to Sponsor)
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computed Tomography
CCI	[redacted]
CCI	[redacted]
e	Electronic
EBRT	Electron Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EFS	Event-Free Survival
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FDA	Food and drug administration
FSA	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practices
GnRH	Gonadotrophin Releasing Hormone
HRQoL	Health-Related Quality of Life

ABBREVIATION	Word Definition
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention to Treat
LH	Luteinising hormone
LHRH	Luteinising Hormone-Releasing Hormone
MCHC	Mean Cell Haemoglobin Concentration
MCH	Mean Cell Haemoglobin
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastases-Free Survival
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NOS	Not Otherwise Specified
OS	Overall Survival
PCSS	Prostate Cancer Specific Survival
PI	Package Insert
PP	Per Protocol
PSA	Prostate Specific Antigen
PSADT	PSA Doubling Time
pT3a	Primary tumour stage 3a
CCI	[redacted]
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
CCI	[redacted]
RP	Radical Prostatectomy
SAE	Serious Adverse Event/Experience
SD	Standard Deviation
SF-36	36-Item Short Form Health Survey
SmPC	Summary of Product Characteristics

ABBREVIATION	Word Definition
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
TMF	Trial Master File
CCI	[redacted]
US	Ultrasound
WBC	White Blood Cell
WHO	World Health Organisation

2 INTRODUCTION

2.1 Disease Review

Prostate cancer is the most common cancer in men, the second most common cause of cancer death and the most common cause of cancer death in men over the age of 70. Its incidence and prevalence have dramatically increased over the past 20 years due to the growing practice of prostate specific antigen (PSA) mass screening of men aged 50 and over. As a consequence, there has been a "stage migration" towards less advanced stages at diagnosis, allowing for more patients to be candidates for radical curative treatment, notably radical prostatectomy (RP) for those with organ-confined disease.

However, the question has arisen as to whether some patients with indolent prostate cancer discovered by systematic screening could be over-treated. Such patients could thus unduly suffer from the relatively common complications of radical treatments, such as urinary incontinence and sexual impotence. As a consequence, prognostic factors have been established as guidance for initial therapeutic decisions [1, 2].

Whereas patients with low or intermediate-risk prostate cancer may benefit from "watchful waiting", those patients with high-risk features should be treated with radical approaches, such as RP or electron beam radiation therapy (EBRT). The usual definition of high risk patients at diagnosis is any of the following [1]:

- Pathologic Gleason score of 8 to10
- PSA ≥20 ng/mL
- Tumour stage T3 to 4

Among these patients, RP is indicated for those with organ-confined tumour (tumour stage 3a (T3a) or lower). Several retrospective and prospective studies have suggested that RP is an appropriate therapy for high-risk, organ-confined tumours [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13], with favourable long-term outcomes, even without adjuvant therapy (Table 1). Importantly, some studies have shown that RP achieves outcomes similar to, or better than, those reported with EBRT [4, 10]. It is important to note that the population defined according to these high-risk criteria is heterogeneous. Patients with Gleason score >8 as the only criterion have a worse outcome than those with T3a as the only criterion [3]. Moreover, patients with two or three criteria have a worse prognosis than those with only one criterion [6].

Table 1 Survival in "High-Risk" Prostate Cancer Patients after Radical Prostatectomy

Author	High-risk definition	N[a]	BRFS (%)			MFS (%)		PCSS (%)	
			3-y	5-y	10-y	5-y	10-y	5-y	10-y
Ploussard 2011 [5]	Gleason 8–10 or PSA>20 ng/mL, ≥T2c	813	-	74.1	-	96.1	-	98.6	-
Walz 2011 [6]	Gleason 8–10 or PSA>20 ng/mL, ≥T2c	887	-	47.4	-	-	-	-	-
Ku 2011 [7]	Gleason 8–10 or PSA>20 ng/mL, ≥T2c	199	61.9	49.2	-	-	-	-	-
Loeb 2010 [8]	Gleason 8–10 or PSA>20 ng/mL, ≥T2c	175	-	-	68	-	84	-	92
Masson-Lecomte 2010 [9]	Gleason 8–10 or PSA>20 ng/mL, ≥T2c	138	-	40	-	-	-	-	-
Arcangeli 2009 [10]	Gleason 8–10 or PSA>20 ng/mL, ≥T2c	122	69.8	-	-	-	-	-	-
Hsu 2010 [11]	T3	164	-	50.4	43	79.7	68.7	93.4	80.3
Oefelein 1997 [12]	"High grade" and ≥T2c	116	-	83 (T2c) 34 (T3)	53 (T2c) 22 (T3)	96 (T2c) 81 (T3)	96 (T2c) 62 (T3)	-	93 (T2c) 78 (T3)
Gerber 1996 [13]	"Grade 3"	N/A	-	-	-	-	52	-	77

BRFS, biochemical relapse-free survival; MFS, metastasis-free survival; N, number of patient; N/A, not available; PCSS, prostate cancer specific survival; T, tumour stage; y, year;

a Most studies specified that patients with adjuvant hormone therapy were to be excluded.

2.2 Compound Review

Triptorelin, a synthetic decapeptide (pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH2), is a gonadotrophin releasing hormone (GnRH) analogue. Studies in animals and man have shown that continued administration of triptorelin exerts, after a short initial stimulation, an inhibitory effect on the gonadotropin secretion with consequent suppression of testicular and ovarian hormonal secretion.

Triptorelin acts by stimulating the pituitary, causing a decrease in the secretion of the gonadotropins, luteinising hormone (LH) and follicle stimulating hormone (FSH). After the first administration there is a transient increase in plasma testosterone levels ("flare-up"), which then decreases to castration levels after approximately 20 days. Castration levels are maintained for as long as the product is administered. Following intramuscular injection, a peak in plasma triptorelin is observed approximately 3 hours after injection, gradually decreasing over the first month after the initial administration. Circulating levels remain stable for 3 months with subsequent injections every 3 months.

Triptorelin is available under a variety of tradenames and in different formulations. It is approved for treatment of locally advanced, and metastatic prostate cancer,

endometriosis, uterine fibromyomas, breast cancer, female infertility, and central precocious puberty (onset before 8 years in girls and 10 years in boys).
Further details can be found in the Summary of Product Characteristics (SmPC) or the Investigator's Brochure where applicable.

2.3 Clinical Trial Rationale

In contrast to the setting of low risk patients, for whom the concern is to avoid over-treating, the concern with high-risk patients is to avoid "under-treating" them, and as such decrease the rate of relapse after initial radical therapy. The question of the benefit of neoadjuvant or adjuvant therapy before or after radical therapy, respectively, is therefore crucial.
The benefit of early adjuvant androgen deprivation (AD) in high-risk patients has been demonstrated after EBRT [14, 15, 16] and is considered as a standard of care [1, 2]. However, there is no scientific evidence for the benefit of adjuvant AD after RP (except for patients with N+ disease) [17], and this treatment approach is not officially recommended [1, 2, 14]. There are data suggesting that RP alone could be superior to EBRT alone and equivalent to EBRT plus AD [4]. Although many patients worldwide with high-risk prostate cancer already receive early androgen suppression after RP based upon the extrapolation of results observed after EBRT, the real benefit and benefit/risk ratio of AD after RP remains to be established in prospective randomised studies.
The present study is designed to assess the benefit of early adjuvant castration with triptorelin for 9 months after RP versus active surveillance, in Chinese and Russian patients with high-risk prostate cancer.
The Chinese guidelines indicate that after radical surgery, patients with pre-surgical PSA levels of ≥20 ng/mL and Gleason score >7, or having extensive positive surgical margins, should be given hormonal therapy as early as possible. However, this recommendation is not based upon robust scientific evidence, and the present study is also designed to confirm the anticipated benefit of early AD. Therefore, such patients with positive margins, who require additional treatment after RP (EBRT plus AD), and who could raise specific therapeutic issues outside of the scope of the present study will not be included. In addition, patients with undetectable post-RP PSA, a criterion which will limit the rate of positive margins, will be selected. The study will not include patients with pathologically positive lymph nodes after RP with lymph node dissection, for whom there is sufficient evidence of the benefit from AD [17] and who will be given AD outside the context of a clinical trial.
The primary efficacy endpoint is biochemical (PSA) relapse-free survival (BRFS). However, it should be noted that the clinical significance of biochemical failure is equivocal, since PSA elevation may precede the onset of metastases by years. In high-risk patients, metastasis-free survival (MFS) could be as high as 60%, 3 years after PSA relapse [18]. Moreover, hormonal intervention at first PSA increase is controversial [19] and not officially recommended [1, 2], except in the case of local symptoms, concurrent occurrence of metastases, or rapid PSA doubling time (PSADT) <3 months [1]. Event-free survival (EFS) or MFS would be more clinically relevant primary endpoints than BRFS. However, the high MFS probability at 5 years after RP (Table 1) and the fact that most patients will receive AD at the time of biochemical recurrence, according to institutional guidelines,

resulted in the selection of BRFS as a realistic primary endpoint to show a significant difference within the follow-up period of this study (3 to 5 months after RP).

The conventional definition of PSA failure is PSA >0.2 ng/mL, confirmed by a second measurement. This definition could be considered very restrictive and unjustified from a practical perspective and has been challenged, especially for clinical trials [20]. Nevertheless, the standard definition has been maintained, taking into account: (1) that all patients will have undetectable PSA levels at study entry and (2) that the decision to start and when to start AD will be left to the Investigator's judgment and institutional standard of care.

Although the duration of adjuvant and neoadjuvant hormonal therapy given after radiotherapy has been studied by several groups [1, 5, 16], the optimal timing and the duration of hormonal therapy administered after RP are still controversial and to our knowledge, no recommendation exists. According to Messing et al, early AD treatment after RP improves survival and reduces the risk of recurrence in patients node-positive PC [17]. Moul et al showed in their retrospective observational multicentre database analysis that early hormonal therapy delayed clinical metastasis in patients with a pathological Gleason sum >7 or PSADT of 12 months or less [19].

The current study is designed to evaluate the effectiveness of the AD induced by the triptorelin, a GnRH analogue, given within 8 weeks after RP for a duration of 9 months.

3 STUDY OBJECTIVES

3.1 Primary Study Objective

To assess the benefit of immediate adjuvant chemical castration after RP in patients with high-risk prostate cancer expressed as BRFS.

3.2 Secondary Study Objectives

- To compare the two arms in terms of:
  - EFS, Overall Survival (OS), Specific-Mortality rate and PSADT
  - Impact on health-related quality of life (HRQoL)
- To assess overall safety of immediate chemical castration.

3.3 Ancillary Exploratory Study Objectives

CCI

4 STUDY DESIGN

4.1 Overview

4.1.1 Population Characteristics

The study will be performed in males aged at least 18 years, with histo-pathologically confirmed adenocarcinoma of the prostate, without positive margins, pathological positive lymph nodes or metastases and with a high risk of disease progression (Gleason score ≥8 by prostatectomy 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 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 arm.

4.1.2 Design

This open, prospective, multicentric, multinational, randomised, controlled study with two parallel arms 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 arms 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.

4.1.3 Structure

Visit 1: Screening Visit

Six weeks (±3 days) after RP, the patient will give written informed consent and will undergo the screening assessments to include a blood sample for serum post-RP PSA level.

Visit 2: Baseline Visit (Randomisation)

Two weeks after the screening visit and no more than 8 weeks (± 3 days) after RP, when post-RP PSA level is available, eligible patients will be randomised to one of two arms, either the triptorelin treatment arm or to the active surveillance arm.

For patients randomised to the triptorelin treatment arm, 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 arm, 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). They will be monitored in the same way as for the triptorelin treatment arm.

Visits 3 to 14: Monitoring Period

All randomised patients (in both arms) will be followed every 3 months (± 1 week) to monitor the occurrence of BR and/or clinical disease progression over a period of 36 months after randomisation (from Visit 3 to Visit 14).

Disease progression is defined as BR and/or clinical disease progression (whichever occurs first):

- BR is defined as the first elevated PSA value >0.2 ng/mL confirmed by a second measurement recorded 4 to 6 weeks later. The time-point at which the first PSA value above 0.2 ng/mL is recorded, will be deemed to be the time of BR.
- 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).

Any patient (in either arm) who has disease progression at any time will receive appropriate medical care from the Investigator. New/additional therapy (for example radiation therapy, surgical castration, or hormonal treatment) will be proposed according to the Investigator's decision and in line with local standard of care. In both arms and depending on the time of occurrence of disease progression, the patient's visit schedule will be as follows:

- If BR and/or clinical disease progression occurs before 36 months, the patient will continue to be monitored until 36 months post-randomisation (Visit 14) at which point he will be considered to have completed the study.
- If at 36 months (Visit 14), the patient has not shown any sign of BR and/or clinical disease progression, and if the statistically required 61 BRs were not observed at the global study level, he will enter the follow-up period.

Post-Visit 14: Follow-up Visits:

If at 36 months post-baseline (at Visit 14), the patient does not have BR and/or clinical disease progression and if the statistically required 61 BRs are not observed at the global study level, he will continue to be followed every 3 months until:

- He has a BR and/or clinical disease progression
- Or, the 61 required BRs are observed on the global study level.

PSA levels, physical examinations and clinical disease progression assessments (where deemed necessary by the Investigator and in accordance with local standards of care) will continue to be performed at each follow-up visit to monitor disease progression.

The study will be considered to be terminated when:

- All included patients have completed their minimum monitoring period of 36 months.
- And, when 61 BRs are observed at the global study level.

Study Completion/Early Withdrawal Visit:

Patients who have disease progression (BR and/or clinical disease progression) within 36 months (event documented before Visit 14) will continue to be monitored until Visit 14 which will be considered as the Study Completion Visit.

Patients who have disease progression after 36 months (event documented during or after Visit 14) will be considered to have completed the trial. Their last study visit would be the visit when disease progression is documented.

After 36 months, patients who do not have disease progression during the whole study will be considered to have completed the trial once the statistically required 61 BR events occur on the study global level.

At any time during the study and for any reason, in case of early withdrawal/discontinuation, the Investigator should perform a last monitoring/follow-up visit considered as the early withdrawal visit.
Figure 1 describes the different scenarios of the schedules of patient visits. Figure 2 provides an overview of the study. See Section 7.1 for the schedule of study assessments.

Figure 1 Scenarios of Schedules of Patient Visits

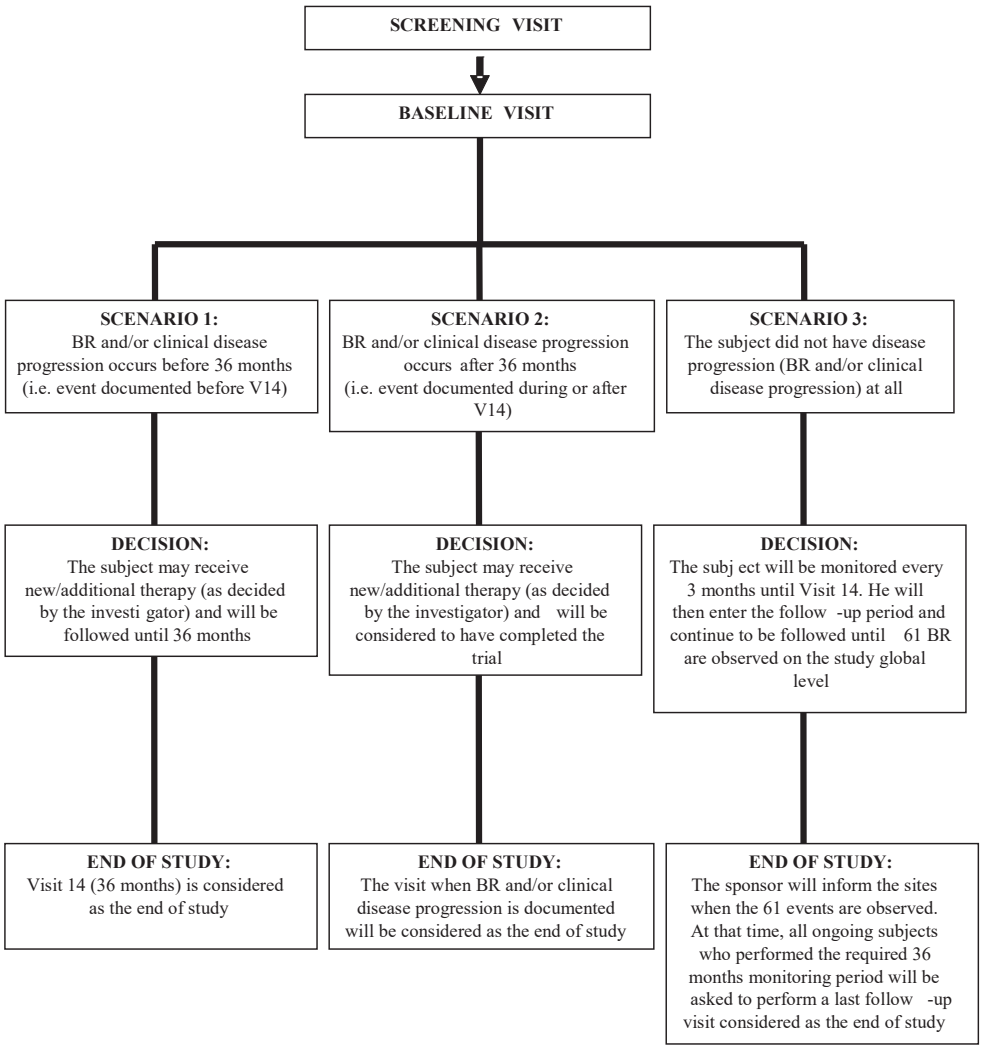
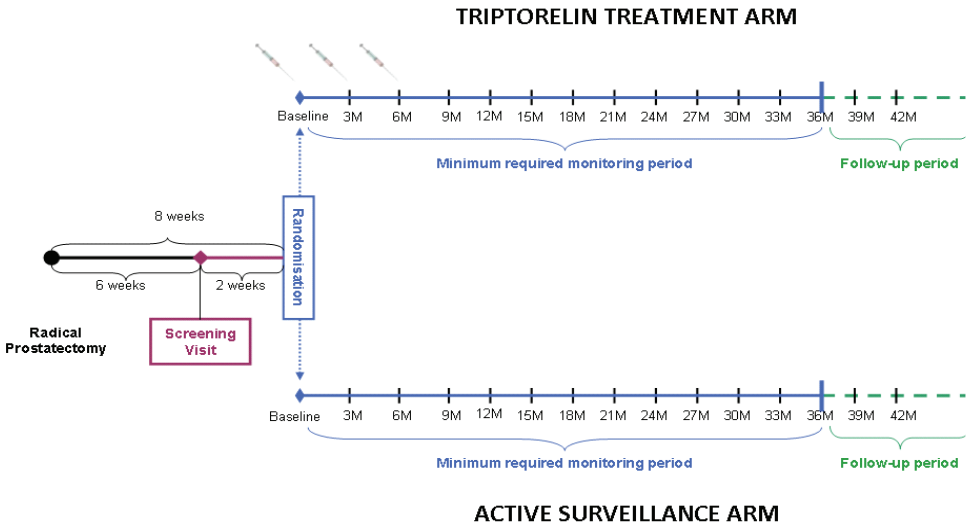


Figure 2 Study Flow Chart



4.1.4 Stopping Rules and Discontinuation Criteria

Patients will be discontinued from study medication (triptorelin) in the event of unacceptable toxicity, evidence of lack of castration at 3 Months/Visit 3 (documented by serum testosterone ≥50 ng/dL (or ≥0.50 ng/mL) confirmed by a second elevated serum testosterone level at least 2 weeks later).

Patients will be discontinued from the study at the study cut-off date, or in the event of death, patient withdrawal of consent, lost to follow-up or noncompliance with the protocol.

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.

Only one reason for withdrawal must be recorded in the case report form (CRF). All Adverse events (AEs) leading to patient withdrawal should be followed until resolution unless confirmed by the Investigator that the event is not going to resolve. Patient withdrawal criteria are detailed in Section 6.4

4.1.5 Early Study Termination

The Sponsor may terminate this study at any time. Reasons for termination may include but are not limited to, the following:

- The incidence or severity of AEs in this or other studies point to a potential health hazard for trial patients
- Insufficient patient enrolment
- Any information becoming available during the study that .substantially changes the expected benefit risk profile of the study treatments

4.2 Endpoints

4.2.1 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint will be BRFS as defined for each patient by the period of time from randomisation to time of BR.

Biochemical Relapse (BR) 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.

BRFS data will be censored on the date of the last assessment on study for patients who do not have BR or on the date of clinical disease progression for those who progress before BR while on study or on the date of death for those who die before BR while on study (of any cause).

Secondary efficacy endpoints

- EFS as defined for each patient as the period of time from randomisation to time of first diagnosed locoregional disease recurrence (positive biopsy and/or node involvement) or first metastases (bone or visceral) documented by relevant standard investigations (US-guided biopsy, X-ray, CT scan, or MRI-guided biopsy) or death from any cause.
- OS defined as the time between randomisation and death from any cause.
- Disease-specific mortality measured as the time between randomisation and death related to prostate cancer.
- PSADT defined as the time 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.
- Serum testosterone in the triptorelin arm at Baseline, 3, 6 and 9 months.
- Health-Related Quality of Life (HRQoL) assessed using the Functional 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.

4.2.2 Exploratory Endpoints

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4.2.3 Safety Endpoints

Signs and symptoms, incidence and severity of all AEs, regardless of relationship to the study drug, graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0, including serious AEs (SAEs) and treatment discontinuations due to toxicity will be monitored from the time that the patient gives informed consent until

Visit 5/Month 9 (three months after the last injection for those patients in the triptorelin arm). After this period, only AEs/SAEs related to triptorelin will be reported.

4.3 Justification of Design

The rationale for the present study assessing the benefit of early adjuvant ADT in men with high risk features/locally advanced prostate cancer was based on the evidence derived from adjuvant ADT in a radiation therapy setting.
Indeed, several studies on adjuvant ADT with a definitive radiation therapy have shown an improvement in disease-free survival in patients with high risk/ locally advanced prostate cancer.
For patients undergoing surgery, the benefit of ADT and its timing as adjuvant hormonal therapy or at PSA relapse, is still a subject of debate. Little clinical evidence exists to date. Furthermore long-term survival outcomes for these patients primarily treated with RP are good, therefore the choice of "biochemical relapse" as a primary endpoint is justified.
An open, prospective, multicentric, randomised, controlled study with two parallel arms, with 5 years study duration is appropriate to address the above clinical question. See also Section 2.3 for additional information.

4.3.1 Study Population for Analysis

Patients with high-risk features/locally advanced prostate cancer who undergo to RP. Patients at high risk of disease progression are defined as those having at least one of the following features: pre-RP PSA ≥20 ng/mL and/or Gleason ≥8 (RP Specimen) and/or pT3a.
See Section 6.2 for detailed information of patient inclusion and exclusion criteria.

4.3.2 Study Duration

The anticipated recruitment period of this study is 2 years. Screening will be performed up to 2 weeks before randomisation. For each patient, study participation is planned to be at least 36 months.
The overall duration of the study will be approximately 60 months. The study will be considered to have started when the first patient has provided signed informed consent, and will be considered to have finished after the last patient has completed the last follow-up visit.
Where possible, all randomised patients will be monitored every 3 months, over at least a period of 36 months, after randomisation. 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. See Section 4.1.3 for further details.
The study will be considered to be terminated when:

- All included patients have completed their minimum monitoring period of 36 months
- And, when 61 BRs are observed on the study global level.

4.3.3 Justification of Exploratory Endpoints

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5 COMPLIANCE WITH GOOD CLINICAL PRACTICE, ETHICAL CONSIDERATIONS & INFORMED CONSENT

5.1 Compliance with Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) [32] Good Clinical Practice (GCP) guidelines, FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, this study will adhere to all local regulatory requirements.

Before initiating a trial, the Investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the trial protocol/amendment(s), written informed consent form, any consent form updates, patient emergency study contact cards, patient recruitment procedures (e.g. advertisements), any written information to be provided to patients and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect patient safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

5.2 Informed Consent

Prior to study entry, the Investigator, or a person designated by the Investigator, will explain the nature, purpose, benefits and risks of participation in the study to each patient, patient's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the patient entering the study (before initiation of any study-related procedure and administration of the investigational medicinal product [IMP]). Sufficient time will be allowed to discuss any questions raised by the patient.

The Sponsor will provide a sample informed consent form. The final version controlled form must be agreed to by the Sponsor, and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the patient. Each patient's original consent form, personally signed and dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled patients with a copy of their signed informed consent.

The consent form may need to be revised during the trial should important new information become available that may be relevant to the safety of the patient or as a result of protocol amendments. In this instance approval should always be given by the IEC/IRB. It is the Investigator's responsibility to ensure that all patients subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Patients who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The Investigator should, with the consent of the patient, inform the patient's primary physician about their participation in the clinical trial.

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[redacted]

6 STUDY POPULATION

6.1 Screening Log and Number of Patients

Each Investigator will maintain a record of all patients who were considered eligible for entry into the study but who were not enrolled. For each patient, the primary reason for exclusion will be recorded.

Each Investigator will also maintain a record of all patients enrolled into the study (i.e., who signed the informed consent form). In the event that a patient randomised to the triptorelin treatment arm does not receive triptorelin, the primary reason will be recorded.

It is planned to recruit approximately 226 patients at approximately 10 centres in Russia and China. Section 11.3 provides a discussion of sample size.

6.2 Inclusion Criteria

All patients must fulfil the following:

(1) Provide written informed consent by the patient prior to any study-related procedure
(2) Men aged ≥18 years
(3) Histo-pathologically confirmed adenocarcinoma of the prostate
(4) Radical Prostatectomy with curative intent performed no more than 8 weeks before randomisation
(5) 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)
(6) Post-RP PSA levels ≤0.2 ng/mL at 6 weeks.
(7) Eastern cooperative oncology group (ECOG)/world health organisation (WHO) performance status of 0 to 1

6.3 Exclusion Criteria

Patients will not be included in the study if any of the following apply:

(1) Has evidence of lymph nodes or distant metastasis
(2) Has positive margins
(3) Has evidence of any other malignant disease, not treated with a curative intent
(4) Previously received or is currently receiving any treatment of prostatic cancer besides the concerned RP
(5) Had a surgical castration
(6) Has a life expectancy of <5 years
(7) Suffers from a significant comorbidity or an untreated infection
(8) Is likely to require treatment during the study with drugs that are not permitted by the study protocol
(9) 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
(10) Was treated with any investigational drug within 4 weeks before the study entry
(11) 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
(12) Is unable to undergo regular follow-up
(13) 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

(14) Has a history of, or known current, problems with alcohol or drug abuse.

6.4 Patient Withdrawal Criteria

If one or more of the following occurs, the patient will be discontinued from study medication if randomised in the triptorelin arm:

- Unacceptable toxicity linked to the treatment
- Evidence of lack of castration at 3 Months/Visit 3 (documented by serum testosterone ≥50 ng/dL ≥0.50 ng/mL) confirmed by a second elevated serum testosterone level at least two weeks later).

If one or more of the following occurs, the patient will be withdrawn from the study:

- The study cut-off date
- Death
- Withdrawal of consent
- Lost to follow-up
- Noncompliance with the protocol

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

No patients will be replaced or enrolled more than once.

All efforts should be made to contact patients to maintain adequate follow-up.

Reason for withdrawal from treatment and/or study, and the date of withdrawal should be documented.

Whenever possible, the tests and evaluations planned every 3 months over the 36 months post-RP (see schedule of assessments, Section 7.1) should be performed. In particular at least one assessment should be performed for any patient withdrawing during the 9 months of triptorelin treatment, to obtain all safety data.

Following discontinuation from the study, there is no study-specific provision of further treatment and additional medical care of the patients once their participation in the trial has ended.

6.5 Discontinuation/Withdrawal Procedures

If the patient is withdrawn from the study (ceases participation in the study before completion of the assessments planned in the protocol), the primary reason should be recorded in the CRF. Withdrawal due to AEs should be distinguished from withdrawal due to insufficient efficacy.

The Investigator will provide or arrange for appropriate follow-up (if required) for patients withdrawing from the study treatment, and will document the course of the patient's condition. When a patient withdraws due to an AE, the Investigator should follow the procedures documented in Section 10 to assess the safety of triptorelin.

Any patient (i.e. in both arms) who develops BR and/or clinical disease progression (whichever occurs first) at any time, will receive the appropriate medical care from his Investigator. New/additional therapy (such as radiation therapy, surgical castration, or hormonal treatment) will be proposed to him at the decision of the Investigator and in line with local standard of care.

7 METHODOLOGY

7.1 Study Schedule

The schedule of observations and assessments during the study are summarised in Table 2.

Table 2 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
CCI															
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 [l]	X	X	X	X	X	X [l]	X [l]	X [l]	X [l]	X [l]	X [l]	X [l]	X [l]	X [l]	X [l]

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	XX
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; CCI

a Only for the triptorelin adjuvant treatment arm (± 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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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 arm. After this visit, only AEs and SAEs related to triptorelin according to Investigator's judgement should be reported.

7.2 Study Visits

7.2.1 Screening Visit (Visit 1) Week –2 (±3 Days)

Screening (Visit 1) will be performed 6 weeks (±3 days) after RP. Written informed consent must be obtained prior to enrolment when the following assessments will be performed:

- Eligibility check (inclusion/exclusion criteria)
- Demography (country, date of birth, sex, ethnic origin/race)
- Prostate Cancer history (prior to RP: date of first histological diagnosis, Gleason score, TNM staging, last available PSA level, last available testosterone level)
- Radical Prostatectomy procedure (date, lymphadenectomy procedure details, pathological features (Gleason Score and TNM staging))
- Significant Medical or Surgical history (including ongoing medical history other than prostate cancer related)
- Physical examination
- Blood sampling for PSA level, haematology and biochemistry

7.2.2 Baseline (Visit 2) Day 1

At the Baseline Visit (Visit 2), 2 weeks after the screening visit and no more than 8 weeks (±3 days) after RP, when post-RP PSA level is available, eligible patients will be randomised to one of two arms. During this visit, the following procedures will be performed (for patients in the triptorelin arm they must be performed prior to drug administration):

- Physical examination
- Vital signs (heart rate, blood pressure [sitting], height and weight)
- ECOG/WHO performance status assessment
- Eligibility check (inclusion/exclusion criteria)
- Randomisation
- Blood sampling for testosterone level (in triptorelin treatment arm only) [redacted]

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- Review of pre-treatment AEs and new or changed concomitant medications/nondrug therapy
- HRQoL questionnaires (FACT-P questionnaire and SF-36 health survey)
- Triptorelin injection, for patients randomised to the triptorelin treatment arm only.

7.2.3 Monitoring Period (Visits 3 to 14)

The patient monitoring visits should be performed every 3 months (±1 week) for a period of 36 months post-randomisation (Visits 3 to Visit 14) for all patients, unless otherwise indicated (for patients in the triptorelin arm, the assessments must be performed prior to drug administration):

- Physical examination
- ECOG/WHO performance status assessment at Months 9, 24, and 36

- Blood sampling for PSA level, every 3 months (note that the elevated PSA concentration >0.2 ng/mL must be confirmed by a second measurement performed 4 to 6 weeks later. No confirmation test is required after evidence of disease progression (BR and/or clinical disease progression):
  - If the first disease progression is a BR, for the following PSA rises, no confirmation test is required.
  - If clinical disease progression occurs before BR, no PSA rise confirmation test is required neither
- Blood sampling for testosterone level, at Months 3, 6 and 9 (in the triptorelin treatment arm only). Evidence of lack of castration will be evaluated at Month 3/Visit 3 documented by serum testosterone ≥50 ng/dL (≥0.50 ng/mL) and must be confirmed by a second elevated serum testosterone level at least two weeks later. For the other testosterone assessment time points (Baseline, 6 and 9 months), no confirmation test is required.
- If lack of castration is confirmed at Visit 3, the testosterone sampling at Visit 4 and Visit 5 are not required.
- Blood sampling for haematology and biochemistry, at Month 9 (Visit 5)

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- Clinical disease progression assessments (US, biopsy, X-ray, CT scan, MRI, etc.) can be performed at any time during the study at the Investigator's discretion and as per local standard care.
- HRQoL questionnaires (FACT-P questionnaire and SF-36 health survey), at Months 9, 24 and 36.
- Documentation of new or changed concomitant medications and nondrug therapy, including documentation of new/additional therapy, if any.
- Evaluation of existing and new AEs and symptoms: AEs will be collected until Visit 5, after this visit, only AEs and SAEs related to triptorelin according to Investigator's judgement should be reported.
- Triptorelin injection at Months 3 and 6 (±7 days) only for patients randomised to the triptorelin arm.
- Survival status.

7.2.4 Follow-up Period (>36 Months After Randomisation)

For any patients followed beyond 36 months post-randomisation, the following assessments should be performed:

- Physical examination should be performed every 3 months
- Blood sampling for PSA level should be performed every 3 months (note that the first PSA value that is >0.2 ng/mL must be confirmed by a second

measurement performed 4 to 6 weeks later. For any following PSA rises, no confirmation retest is required. In cases where clinical disease progression occurs before BR, no confirmation retest is required).

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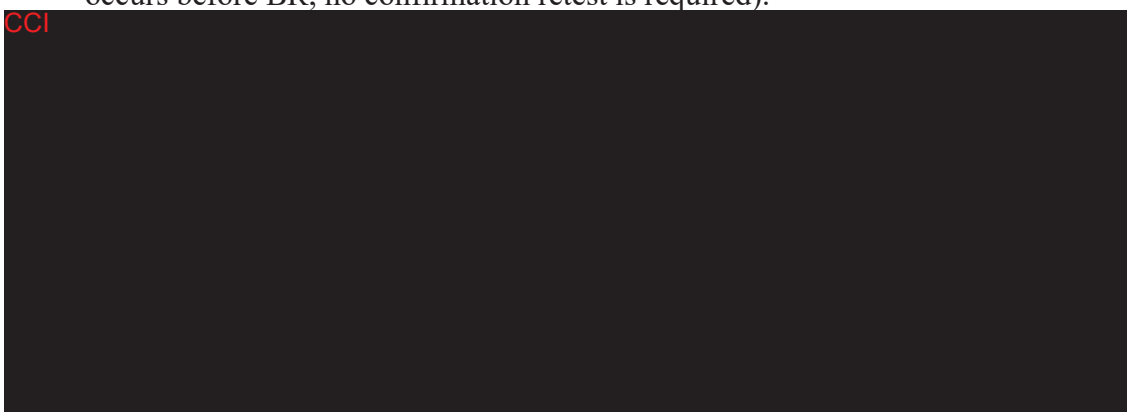


- Clinical Disease Progression assessments (US, biopsy, X-ray, CT scan, MRI, etc.) can be performed at any time during the study at the Investigator's discretion and as per local standard care
- Documentation of new or changed concomitant medications and nondrug therapy
- Evaluation of existing and new AEs and symptoms: at this level, only AEs and SAEs related to triptorelin according to investigator's judgement should be reported.
- Survival status.

7.2.5 Study Completion or Early Withdrawal Visit

Patients who have a disease progression (BR and/or clinical disease progression) before 36 months (i.e. event documented before Visit 14) will continue to be monitored until Visit 14, which will be considered as their study completion visit.

Patients who have disease progression (BR and/or clinical disease progression) after 36 months (i.e. event documented during or after Visit 14) will be considered to have completed the trial. Their last study visit would be the visit when disease progression is documented.

After 36 months, patients who do not have disease progression during the whole study will be considered to have completed the trial once the statistically required 61 BR events occur.

At any time during the study and for any reason, in cases of early withdrawal/discontinuation, the Investigator should perform a last monitoring/follow-up visit.

The required assessments are similar to those of any follow-up visit:

- Physical examination
- Blood sampling for PSA level
- Clinical Disease Progression assessments (US, biopsy, X-ray, CT scan, MRI, etc.), as appropriate
- Documentation of new or changed concomitant medications and nondrug therapy
- Evaluation of existing and new AEs and symptoms.
- Survival status

8 STUDY EVALUATIONS

For the timing of assessments during the study, refer to the study schedule in Section 7.1.

8.1 Efficacy Endpoints and Evaluations

For the timing of evaluations during the study, refer to the study schedule in Section 7.1.

8.1.1 Primary Efficacy Endpoint and Evaluations

Biochemical Relapse-Free Survival (BRFS) is defined for each patient by the period of time from randomisation to time of BR.

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.

BRFS data will be censored on the date of the last assessment on study for patients who do not have BR or on the date of clinical disease progression for those who progress before BR while on study or on the date of death for those who die before BR while on study (of any cause).

PSA levels will be evaluated on a per patient basis and assessed in terms of the overall population (see Section 11 for further details). Blood samples to obtain the required serum volume for PSA testing will be taken every 3 months. Testing will be performed in a central laboratory designated by the Sponsor. Details of the methodology and reference ranges will be provided in the Trial Master File (TMF) and the laboratory manual.

8.1.2 Secondary Efficacy Endpoints and Evaluations

- EFS as defined for each patient as the period of time from randomisation to time of first diagnosed locoregional disease recurrence (positive biopsy and/or node involvement) or first metastases (bone or visceral) documented by relevant standard investigations (US guided biopsy, X-ray, CT scan, or MRI guided biopsy) or death from any cause.
- OS defined as the time between randomisation and death from any cause.
- Disease-specific mortality measured as the time between randomisation and death related to prostate cancer.
- PSADT defined as the time 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.
- Serum testosterone in the triptorelin arm at Baseline, 3, 6 and 9 months.
- Health-Related Quality of Life (HRQoL) 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.

<u>Clinical disease progression assessments</u>

These can be performed to identify the presence of locoregional disease recurrence (positive biopsy and/or node involvement) or metastases (bone or visceral), using standard investigations (US, biopsy, X-ray, CT scan, MRI, etc.), performed according to the Investigator's discretion and as per site standard of care.

Disease-specific mortality
This will be determined according to documented cause of death being disease progression.
PSA
See Section 8.1.1 for details of PSA evaluations.
Testosterone
Blood samples to obtain the required serum volume for testosterone testing will be collected at Baseline, and at Months 3, 6 and 9 in patients treated in the triptorelin arm only (before the triptorelin injection). Testing will be performed in a central laboratory designated by the Sponsor. Standard testosterone blood sample collection procedures should be used. Details of the methodology and reference ranges will be provided in the TMF and the laboratory manual.
HRQoL
Each patient will complete the FACT-P HRQoL questionnaire [33], version 4 and the SF-36 health survey, version 2 at Baseline and at Months 9, 24 and 36. Patients will be provided with a paper version of each questionnaire in the local language, which will be completed during the visit.
All secondary endpoint evaluations will be performed on a per patient basis and assessed in terms of the overall population (see Section 11 for further details).

8.2 Safety Endpoints and Evaluations

8.2.1 Safety Endpoints

Signs and symptoms, incidence and severity of all AEs, regardless of relationship to the study drug (graded according to the NCI-CTCAE, version 4.0), including SAEs and treatment discontinuations due to toxicity will be monitored from the time that the patient gives informed consent until Visit 5/Month 9 (three months after the last injection for those patients in the triptorelin arm). In addition, data relating to related AEs and SAEs will continue to be monitored and recorded after Visit 5/Month 9 until the end of the study.

8.2.2 Adverse Events, Signs and Symptoms

AEs will be monitored from the time that the patient gives informed consent until Visit 5/Month 9 (three months after the last injection is administered for those patients in the triptorelin arm). In addition, data relating to related AEs and SAEs will continue to be monitored and recorded after Visit 5/Month 9 until the end of the study. AEs will be elicited by direct, nonleading questioning at each study visit or by spontaneous reports. Further details for AE reporting can be found in Section 10.

8.2.3 Physical Examination

A physical examination will be performed by a physician (Investigator or designee). If in the opinion of the Investigator there are any clinically significant changes in the physical examination findings (abnormalities) they will be recorded as AEs.

8.2.4 Vital Signs

Height, weight, heart rate, and blood pressure (sitting) will be measured at Baseline.

8.2.5 Clinical Laboratory Tests

Blood samples for clinical laboratory tests will be taken at Screening (Visit 1) and Month 9 (Visit 5), and will consist of the following:

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.

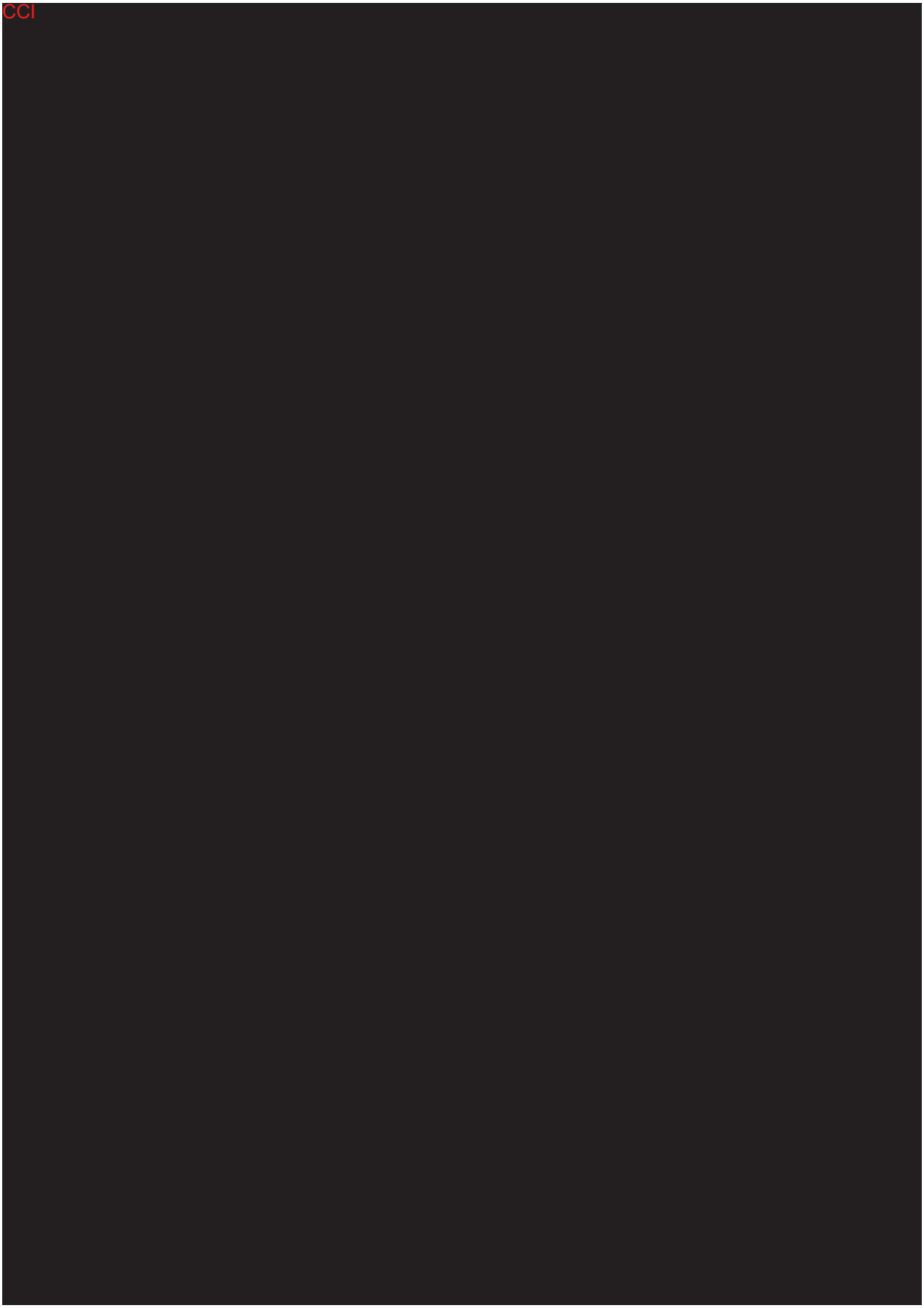
Biochemistry: urea, creatinine, total bilirubin, chloride, bicarbonate, sodium, potassium, calcium, inorganic phosphate, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), albumin, total protein, total cholesterol, triglycerides, and fasting glucose.

Clinical laboratory tests will be performed in a central laboratory designated by the Sponsor. Standard haematological and biochemical blood sample collection should be used. Details of the methodology and reference ranges will be provided in the TMF.

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the Investigator and the Sponsor's clinical monitor (or his/her designated representative), or until the abnormality is explained by an appropriate diagnosis. See Section 10.2.4 for abnormal laboratory tests that should be recorded as AEs in the eCRF.

8.3 Exploratory Endpoints and Evaluations

CCI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8.4 Total Blood Volume

The required blood volume per assessment is show in Table 3.

Table 3 Total Blood Volume Required During the Study

Assessment	Blood Volume
PSA	When performed alone: 2.5 mL of blood When performed with testosterone and/or biochemistry: 5 mL of blood for all assessments
Testosterone	When performed alone: 2.5 mL of blood When performed with PSA and/or biochemistry: 5 mL of blood for all assessments
Biochemistry	When performed alone : 2.5 mL of blood When performed with PSA/and or testosterone: 5 mL of blood for all assessments
Haematology	2 mL of blood

CCI

Note that :

- The first elevated PSA concentration >0.2 ng/mL must be confirmed by a second PSA concentration >0.2 ng/mL (additional 2.5 mL of blood).

CCI

The total blood volume per patient is variable depending on the time of occurrence of disease progression. The required amount of blood will vary between a minimum

of 64 mL and a maximum of 87 mL for a patient performing the 36 months monitoring period. For any additional visit post-36 months, the volume needed is 2.5 mL of blood for PSA analysis.

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[redacted]

9 STUDY TREATMENTS

9.1 Study Treatments Administered

It is forbidden to use IMP for purposes other than as defined in this protocol. Administration of the IMP will be supervised by the Investigator, or designee.

Pharmaceutical form

Powder and solvent for suspension for intramuscular injection prolonged released form.

Active component

Triptorelin pamoate, as triptorelin 11.25 mg.

Drug name

China: Triptorelin pamoate for injection; 15 mg

Russia: Diphereline® 11.25 mg

Posology and method of administration

Triptorelin will be administered as a hormonal adjuvant to RP for patients randomised to the triptorelin treatment arm. These patients will receive one

intramuscular injection of the product, which will be repeated every 3 months for a total of three injections: at Baseline, 3 and 6 months.
Patients in the active surveillance arm will be treated according to each study centre's standard of care, excluding administration of any method of adjuvant treatment (hormonal treatment and/or surgical castration and/or radiation therapy).
Relapsing patients (BR and/or clinical disease progression) in both arms can receive new/additional therapy, according to the Investigator's decision and the local standard of care.

9.2 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. This identification number is unique and will be composed of five digits: the first two digits will correspond to the site number, and the three other digits will be implemented chronologically depending on patient inclusion. The Investigator will maintain a list of patient numbers and names to enable records to be found at a later date if required.

9.2.1 Randomisation

The Sponsor's randomisation manager who is a statistician independent from the study, will prepare the master randomisation list for this study. The block size of this computer-generated randomisation list will ensure a balanced ratio between the two treatment arms.
After eligibility is confirmed at Visit 2 (Baseline), patients will be assigned a randomisation number and will be randomised in one of two treatment arms ("Triptorelin treatment" or "Active surveillance"). This will be done by opening the first not used treatment allocation envelope in the set allocated to the site. Under no circumstances will the Investigator change the treatment arm allocated to the patient.
Recruitment will stop once 226 patients have been randomised. Randomised patients who terminate their study participation for any reason before starting the treatment will retain their randomisation number (the randomisation number will not be reused). The next patient is given the next randomisation number.
Randomised patients who leave the study early will not be replaced.
The Sponsor's randomisation manager will keep the confidential master list in a secure location. Access to this list must be restricted until authorisation is given for analysis.

9.2.2 Blinding, Emergency Envelopes and Breaking the Blind

This is an open-label study. However, the treatment arm assigned to a randomisation number must be blinded while it is not allocated. Therefore, for each randomisation number, a treatment allocation envelope containing the treatment arm to be considered will be prepared by the Sponsor's randomisation manager.
As soon as a study treatment allocation envelope is opened, specifications are to be written on it, in the pre-printed area (opener's identification, opening date and time and signature). Monitors should routinely check these specifications on the allocated

envelopes and the integrity of all other envelopes. All the study treatment allocation envelopes must be kept in the TMF in the coordinating office at study completion.

9.3 Study Treatment Supply, Packaging and Labelling

A commercial formulation of triptorelin (Diphereline®) will be supplied by Ipsen Pharma. Triptorelin will be supplied as a powder which will be mixed with a 0.8% mannitol solution at the time of administration. A homogeneous suspension will be obtained by mixing and should be injected immediately.

Triptorelin powder will be supplied in a 4 mL glass vial with a rubber stopper and an aluminium cap. Each vial will contain slightly more than 11.25 mg to ensure that the full dose will be administered to the patient. Suspension vehicle (2 mL) will be supplied in a 3 mL capacity glass ampoule. Both products should be stored below 25°C.

Triptorelin will be provided in a pack containing one clear glass vial containing the triptorelin powder, one glass ampoule containing the suspension vehicle, one syringe and two needles.

The core label texts for all packaging units will be translated or adjusted to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. A description of the core text of the IMP labels is displayed below:

- Name, address and telephone number of the Sponsor
- Study number
- Pharmaceutical dosage form
- Route of administration
- Quantity of dose units
- Batch number
- Treatment number
- Randomisation number: information completed on site
- For clinical trial use only
- Investigator Name: information completed on site (the main contact for information on the product, clinical trial)
- Storage conditions
- Expiry date
- Directions for use (reference may be made to the leaflet for the person administering the product)

Triptorelin will be delivered to the investigational sites. A sufficient quantity will be supplied as well as an acknowledgment of receipt form.

The Investigator, or designee, will only dispense triptorelin to patients included in this study and randomised to the triptorelin treatment arm. Dispensing for each patient will be documented in the CRF.

See the SmPC/product leaflet (PL) of the concerned countries for further details.

9.4 Compliance

In the treatment arm, triptorelin will be administered via intramuscular injection by a medically-trained individual. Any incomplete or missed injections will be documented in the CRF including the reason.

Compliance will be assessed by reporting of study drug administration in the patient's record and by the drug accountability forms.

9.5 Study Treatment Storage and Accountability

The Investigator, or an approved representative (e.g. pharmacist), will ensure that triptorelin is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements and will be reconstituted and dispensed by qualified staff members.

All study treatments are to be accounted for on the accountability log provided by the Sponsor. It is essential that all used and unused supplies are retained for verification (by the Sponsor or Sponsor's representative). The Investigator should ensure adequate records are maintained via the accountability log.

In accordance with good manufacturing practice (GMP) guidelines, destruction of the unused and used investigational product once administration has taken place should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation have been accepted. Any destruction should be documented using a certificate of destruction.

9.6 Concomitant Medication/Therapy

No adjuvant treatment with any method (hormonal treatment and/or surgical castration and/or radiation therapy) should be initiated in the active surveillance arm prior to evidence of recurrence (clinical or biochemical).

New/additional therapy (radiation therapy, surgical castration, hormonal treatment, etc.) will be proposed to any patient (in either treatment arm) who develops BR and/or clinical disease progression (whichever occurs first) at any time, according to the local standard of care. Patients are not permitted to receive any other IMP during the study or during the 4 weeks prior to randomisation.

9.7 Treatment of Overdose of IMP

The incidence of overdose during the clinical development of triptorelin is low, with no significant sequelae reported. Based on these data, there is no evidence to suggest an associated risk of overdose with triptorelin treatment. Animal data do not suggest any effects other than those on sex hormone concentration and the consequent effect on the reproductive tract. If overdose occurs, symptomatic management is indicated. Any appropriate treatment of overdose will be determined by the Investigator according to the characteristics of the events and will be recorded in the patient's CRF. An event resulting from an overdose of the trial medication is not considered as serious unless it meets the definition of an SAE and consequently should be reported on the SAE form (see Section 10.4).

10 ADVERSE EVENT REPORTING

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

This definition includes events occurring from the time of the patient giving informed consent until the end of the study (as defined in Section 4.3.2).

10.1 Disease Progression

Natural progression or deterioration of the malignancy under study will be recorded as part of the efficacy evaluation and should not be recorded as an AE/SAE.
Likewise, death due to disease progression will be recorded as part of the efficacy evaluation and will not be regarded as an SAE.
Signs and symptoms should not be reported as AEs/SAEs if they are clearly related to a relapse or an expected change or progression of the baseline malignant disease.
These signs and symptoms should only be reported as AEs/SAEs (depending on the Investigator's judgement) if they are:

- Judged by the Investigator to be unusually severe or accelerated (for stage of malignant disease), or
- If the Investigator considers the deterioration of malignancy-related signs and symptoms to be caused directly by the study drug.

As a rule, if there is any uncertainty about an AE being due solely to the malignancy under study, it should be reported as an AE/SAE as appropriate. This definition includes events occurring from the time of the patient giving informed consent until the end of the study.
Symptoms of disease progression that are not considered to be AEs should be documented in the CRF.

10.2 Categorisation of Adverse Events

10.2.1 Intensity Classification

AEs will be recorded and graded according to the NCI-CTCAE, version 4. In view of meta-analyses, and for conversion purposes, the following conversion mapping will apply if the NCI-CTCAE scale is not available for a given AE:

- NCI-CTCAE Grade 1 corresponds to mild,
- NCI-CTCAE Grade 2 corresponds to moderate,
- NCI-CTCAE Grade 3 corresponds to severe,
- NCI-CTCAE Grade 4 corresponds to life threatening/disabling,
- NCI-CTCAE Grade 5 corresponds to death.

Where:
Mild: symptoms do not alter the patient's normal functioning
Moderate: symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the patient
Severe: symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.
Life-threatening: any event that places the patient at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death. Also see Section 10.4.1.

10.2.2 Causality Classification

The relationship of an AE to the IMP will be classified according to the following:
Related: reports including good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology, positive de-challenge and/or re-challenge) to assume a causal

relationship with the IMP in the sense that it is plausible, conceivable or likely.

Not related: reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with the IMP.

10.2.3 Assessment of Expectedness

The expectedness of an AE/reaction shall be determined by the Sponsor according to the Investigator's Brochure for an unapproved IMP or SmPC or Package Insert (PI) for an authorised medicinal product which is being used according to the terms and conditions of the marketing authorisation.

The reference document for assessing expectedness of AEs/reactions in this study will be the current Investigator's Brochure.

10.2.4 Laboratory Test Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- they result in a change in triptorelin schedule of administration (change in dosage, delay in administration, triptorelin discontinuation),
- they require intervention or a diagnosis evaluation to assess the risk to the patient,
- they are considered as clinically significant by the Investigator.

10.2.5 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the Investigator, in physical examination findings (abnormalities) will be recorded as AEs.

10.2.6 Other Investigation Abnormal Findings

Abnormal objective test findings as judged by the Investigator as clinically significant (e.g., electrocardiogram changes) that result in a change in IMP dosage or administration schedule, or in discontinuation of the IMP, or require intervention or diagnostic evaluation to assess the risk to the patient, should be recorded as AEs.

10.3 Recording and Follow-up of Adverse Events

At each visit the patient should be asked a nonleading question such as: "Do you feel different in any way since starting the new treatment/the last assessment?"

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to triptorelin, will be recorded on the AE page(s) of the CRF up to and including Visit 5/Month 9. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbations of pre-existing illnesses should be recorded according to the NCI terminology if applicable.

AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (i.e., triptorelin or other illness). The Investigator is required to assess causality and record that assessment

on the CRF. Follow-up of the AE, after the date of therapy discontinuation, is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the Investigator and the Sponsor's clinical monitor or his/her designated representative

10.4 Serious Adverse Events

10.4.1 Definitions

All SAEs (as defined below) regardless of treatment group or suspected relationship to IMP must be reported immediately (within 24 hours of the Investigator's knowledge of the event) to the pharmacovigilance contact specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

A SAE is any AE occurring at any dose that:

(1) Results in death;

(2) Is life threatening, that is any event that places the patient at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death;

(3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further);

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;

(5) Results in congenital anomaly/birth defect in the offspring of a patient who received the IMP;

(6) Is an important medical event that may not result in death, be life-threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

Regardless of the above criteria, any additional AE that the Sponsor or an Investigator considers serious should be immediately reported to the Sponsor and included in the corporate SAEs database system.

- Hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- Prolongation of hospitalisation is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the Investigator or treating physician. For protocol-specified hospitalisation in clinical trials, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e., not associated with the development of

a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the Sponsor.

- Pre-planned or elective treatments/surgical procedures should be noted in the patient's screening documentation. Hospitalisation for a pre-planned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

10.4.2 Reporting Requirements

Any SAE must be reported immediately (within 24 hours), independent of the circumstances or suspected cause, if it occurs or comes to the attention of the Investigator at any time from the signing of the informed consent, until Visit 5/Month 9 (three months after the last injection for those patients in the triptorelin arm).

Any SAE with a suspected causal relationship to triptorelin occurring at any other time after Visit 5/Month 9 must be promptly reported.

10.4.3 Mandatory Information for Reporting an SAE

The following information is the minimum that must be provided to the Sponsor's pharmacovigilance contact within 24 hours for each SAE:

- Trial number
- Centre number
- Patient number
- AE
- Investigator's name and contact details

The additional information included in the SAE form must be provided to the Sponsor or representative as soon as it is available. Upon receipt of the initial report, the Sponsor will ask for the Investigator's causality assessment if it was not provided with the initial report.

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

10.4.4 Reporting Exemptions

Relapse or progression of disease that is not worse in terms of time-course or severity of the disease expected in that patient is considered an efficacy outcome parameter (as described in Section 10.1), and is excluded from the definition of an AE/SAE. These events will not be reported as AEs or SAEs.

Tumour-related signs and symptoms will only be recorded as AEs during the trial if they worsen in severity or increase in frequency beyond that normally expected for disease progression as determined by the Investigator.

Death due to disease progression during the study or follow-up period will be regarded as an efficacy endpoint and will not be included as an SAE (see Section 10.1).

10.5 Pregnancy

Since this study will be conducted in men, this is not applicable.

10.6 Deaths

All AEs resulting in death at any time until the end of the study (except those listed in Sections 10.1 and 10.4.4) must be reported as an SAE within 24 hours of the Investigator's knowledge of the event, as described in Section 10.4.2.

The convention for recording death is as follows:

- AE term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction).
- Outcome: fatal.

For AEs leading to death, NCI-CTCAE Grade 5 is the only appropriate grade (see Section 10.2.1). Deaths that cannot be attributed to an NCI-CTCAE term associated with Grade 5 or that cannot be reported within an NCI-CTCAE category as 'Other', have to be reported as one of these four AE options:

- Death not otherwise specified (NOS)
- Disease progression NOS
- Multi-organ failure
- Sudden death.

10.7 Discontinuation/Withdrawal Due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient efficacy of triptorelin (see Sections 6.4 and 6.5).

If triptorelin is discontinued due to an SAE it must be reported immediately to the Sponsor's designated representative (see Section 10.4).

In all cases the Investigator must ensure the patient receives appropriate medical follow-up (see Section 10.3).

10.8 Reporting to Competent Authorities/IECs/IRBs/Other Investigators

The Sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the Competent Authorities (CA), IECs, IRBs and other Investigators concerned by triptorelin. Reporting will be done in accordance with the applicable regulatory requirements.

11 STATISTICAL CONSIDERATIONS

11.1 Patient Classification and Definitions

- **Enrolled patient:** Patient fully informed about the study who has given written informed consent to participate (before any occurrence of trial related procedure)
- **Screened failure patient:** Enrolled patient who fails to fulfil one or more entry criteria and thus does not proceed to the treatment phase of the study. Although not exposed to study medication or treatment approach, they may have been exposed to some study related procedures. Records up to the time of premature termination should be completed including the reason for termination
- **Treated patient :** Enrolled patient who is treated with at least one dose of study medication or followed the treatment approach
- **Randomised patient:** Enrolled patient who is allocated to a treatment group at random.
- **Study Completed patient:** Randomised/Treated patient who has completed all specified phases/assessments of the study.
- **Drop-out:** Randomised/Treated patient who did not complete the study and or treatment.

11.2 Analyses Populations Definitions

- **Screened population:** All patients enrolled
- **Randomised population:** All patients randomised
- **Safety population:** 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.
  Patients will be analysed as treated for the safety analyses.
- **Intention-to-treat (ITT) population:** All randomised patients analysed according to the arm to which they were randomised (i.e. regardless of treatment approach followed)
- **Per protocol (PP) population:** All patients in the ITT population for whom no major protocol violations/deviations occurred

11.2.1 Populations Analysed

The primary analysis based on the primary efficacy endpoint(s) will be performed on the ITT population. Per protocol analyses will only be considered as exploratory. The analyses of safety data will be performed in the safety population.

11.2.2 Patient Allocation and Reasons for Exclusion from the Analyses

The rules for the allocation of patients to each of the analysis populations will be defined and documented during a data review meeting held prior to database lock.

During the data review meeting, based on minor or major protocol violations/deviations, patients may be excluded from the ITT/PP population.
Patients may be excluded from the analyses if one or more of the following violations/deviations occur:

- Randomisation criteria violations
- Inclusion/exclusion criteria violations
- Did not receive any study medication (triptorelin arm only)
- Inadequate compliance of study medication
- Prohibited medication intake
- Deviations from time windows
- Deviations from study medication administration
- No baseline evaluation of PSA
- No valid post-baseline evaluation of PSA
- Other protocol violation/deviations

11.3 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 at 36 months after RP is 40% in high-risk patients (Section 2.1, 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).
It is planned to recruit 226 patients in approximately 10 centres in two countries (China and Russia).

11.3.1 Significance Testing and Estimations

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

11.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external Contract Research Organisation (CRO) managed by the Sponsor's Clinical Development Data Sciences Department.
A reporting and analysis plan (RAP) describing the planned statistical analysis in detail with tables, figures and listings (TFLs) templates will be developed as a separate document.
Statistical evaluation will be performed using Statistical Analysis System (SAS)® (Version 8 or higher).

11.4.1 Demographic and Other Baseline Characteristics

In order to ensure balance of treatment groups, descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic and 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.

11.4.1.1 Homogeneity of Treatment Groups

Homogeneity of treatment groups at baseline will be assessed descriptively, or by 95% confidence interval (CI). No formal statistical significance testing will be performed.

11.4.1.2 Patient Disposition and Withdrawals

The numbers and percentages of patients enrolled and included in the ITT/PP and safety populations will be tabulated by country and centre. The reasons for patient exclusions from each of the populations will also be tabulated. In addition, the numbers of patients who were randomised, discontinued and completed the study will be tabulated by treatment group. Primary reasons for discontinuation of study treatment will be tabulated.

11.4.1.3 Efficacy Evaluation

Primary and secondary endpoints are defined in Section 8.1. The primary efficacy variable is BRFS, which is defined as the time from date of randomisation to first BR. BRFS data will be censored on the date of the last assessment on study for patients who do not have BR or on the date of clinical disease progression for those who progress before BR while on study or on the date of death for those who die of any cause before BR while on study. The primary analyses of BRFS will be performed in the ITT population. A log-rank test (two-sided) will be used to compare BRFS time between the two treatment groups with nominal significance level 0.05 (two-sided). The Kaplan-Meier method will be used to obtain the estimates of median EFS associated with each treatment. The 95% CI of the median event-free time will also be provided. The Cox Proportional hazards model will be fitted to compute hazard ratios and the corresponding 95% CI. The primary analysis will be repeated on the PP population.

To identify which factors are associated with BRFS outcome, Cox proportional hazards regression models will be used. To explore prognostic factors analysis of deviance will be conducted. Each factor will be assessed individually for prognostic value ($p<0.05$) using a univariate Cox model. Factors that are deemed to have prognostic value ($p<0.2$) will be included as covariates in a multivariate Cox model to assess their significance in the presence of other factors. A backward selection process 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 secondary efficacy variables are EFS, OS and PSADT, serum testosterone in the triptorelin-treated arm at 3, 6, 9 months post-RP, and HRQoL measured at 9, 24 and 36-months post-RP.

Time-to-event data will be analysed as the primary efficacy variable. All quantitative variables will be analysed with either analysis of variance (ANOVA) or analysis of covariance (ANCOVA) adjusting for baseline variable score when measured.

Missing data will not be imputed and dropouts will not be replaced. For time-to-event analyses, the handling of patients without the event will be specified separately for each parameter in the RAP.

HRQoL changes from baseline for each scale/dimension will be calculated for each arm at each time point. Missing data imputation rules will be defined in the RAP. Treatment groups will be compared based on ANCOVA adjusting for baseline score and 95% CI will be presented to display treatment effect estimates.

11.4.1.4 Adjustment for Country/Centre Effect

Descriptive analysis will be performed to describe any possible country effect.

11.4.1.5 Safety Evaluation

All safety data will be included in the patient data listings. Analyses and summary tables will be based upon the safety population.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA; latest version available) and will be classified by MedDRA preferred term and system organ class. AE listings will be presented by patient, system organ class and preferred term.

Incidence of all reported AEs, treatment emergent AEs (TEAE) and SAEs will be tabulated by treatment group and overall. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs/TEAEs associated with premature withdrawal of study medication.

A TEAE is defined as any AE that occurs during the active phase of the study if:

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

TEAEs will be flagged (*) in the AEs listings.

Concomitant medication will be coded by using WHO Drug Dictionary (latest version available) and will be summarised by treatment group and overall with the number and percentage of patients receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, SD and range as appropriate) by treatment group and overall will be presented for clinical laboratory tests at each assessment with change from baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented of the number and percentage of patients with low, normal or high values and normal or abnormal exams.

AEs reported by Investigators using the NCI-CTCAE classification (version 4) will be coded using the MedDRA dictionary (latest version available).

Summary incidence tables will be provided, classified by body system, preferred term and associated NCI-CTCAE worst grade. In the event of multiple occurrences

of the same AEs being reported by the same patient, the maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) will be chosen. Dose delays and dose interruptions will be listed by cycle.
Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTCAE criteria

11.5 Subgroup Analyses

If subgroup analyses are deemed necessary, they will be described in the RAP.

11.6 Interim Analyses and Data Monitoring

No interim analysis will be performed.

11.7 Final Analysis

Final analysis will be performed after 61 BR events have been observed.
A total of 61 events are required in the final analysis to demonstrate a 20% absolute improvement in rate of BR with 90% power using a significance level of 0.05.

12 MONITORING PROCEDURES

The Investigator is responsible for the validity of all data collected at the site. The Sponsor is responsible for monitoring this data to verify that the rights and wellbeing of patients are protected, that trial data are accurate (complete and verifiable to source data) and that the trial is conducted in compliance with the protocol, GCP and regulatory requirements.

12.1 Routine Monitoring

Sponsor-assigned monitors will conduct regular site visits. The Investigator will allow direct access to all relevant files (for all patients) and clinical trial supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.
The site must complete the eCRFs within 5 days of the patient's visit and on an ongoing basis to allow regular review by the study monitor, both remotely via the internet and during site visits. The central study monitor at Ipsen will use functions of the Electronic Data Capture (EDC) system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.
Whenever a patient name is revealed on a document required by the Sponsor (e.g., laboratory print-outs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the patient number as identification.

13 STUDY MANAGEMENT

13.1 Inspections and Auditing Procedures

Authorised personnel from external CAs and Sponsor-authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the Sponsor.
Auditors and inspectors must have direct access to study documents and site facilities as specified in section 12.1, and to any other locations used for the purpose of the study in question (e.g., laboratories).

In the event of the site being notified directly of a regulatory inspection, the Investigator must notify the Sponsor representative as soon as possible, to assist with preparations for the inspection.

13.2 Data Recording of Study Data

In compliance with GCP, the medical records/medical notes, etc., should be clearly marked and permit easy identification of a patient's participation in the specified clinical trial.

The Investigator must record all data relating to protocol procedures, triptorelin administration, laboratory data, safety data and efficacy ratings on the eCRFs provided for the study. The Investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF.

FACT-P and SF-36 patient questionnaires will be printed and completed using paper versions.

The Investigator must, as a minimum, provide an electronic signature (e-signature) to the whole case book to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF after a form has been electronically signed, the Investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

13.3 Source Data Verification

The FDA 21 CFR Part 11, is a regulation which provides criteria for acceptance by the FDA, under certain circumstances, of electronic records, e-signatures and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures on paper.

As required by GCP, the Sponsor assigned monitor must verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.

The source documents must, as a minimum, contain the following:

- A statement that the patient is included in a clinical trial
- The date that informed consent was obtained prior to participation in the study
- The identity of the study, visit dates (with patient status)
- Demographics
- Diagnosis and eligibility criteria,
- Results of physical examinations, vital signs
- Medical history
- Required laboratory test
- Clinical disease progression assessments, if any
- HRQoL questionnaires administration
- Triptorelin administration
- Associated concomitant medication
- All AEs with start/end dates
- The date the patient completed or withdrew from the study and the reason for withdrawal, if applicable

Definition for source data and source documents are given below:

- **Source Data:** All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). [ICH GCP Section 1.51]
- **Source Documents:** Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). [ICH GCP Section 1.52]

The patient must have consented to their medical records being viewed by Sponsor-authorised personnel, and by local, and possibly foreign, CAs. This information is included in the informed consent.

13.4 Data Quality

Monitored eCRFs will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance by the CRO assigned by Data Management group.

Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the Investigator by the monitor for clarification/correction. The Investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

13.5 Data Management

Electronic Data Capture will be used for collecting patient data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only Sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Paper CRFs will be available to ensure business continuity in case the eCRFs are unavailable at the site for a prolonged period, they will be used only after prior permission is gained from the Sponsor.

Data management will be conducted by a CRO, directed by the Sponsor's Data Management Department. All data management procedures will be completed in accordance with Ipsen and the contracted CRO Standard Operating Procedures (SOPs). Data will be monitored at the Investigator site (for further details see

Section 12 and any documentation removed from the Investigator site(s) will be tracked by the CRO and the monitor (e.g. patient questionnaires).

The Sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The Investigator will receive their data, from the clinical trial, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries raised within the EDC system during the data management process will also be tracked by the contracted data management CRO. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The Sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the Sponsor's pharmacovigilance department (and vice versa).

The coding of AEs, medical history and concomitant medication terms will be performed by the contracted CRO and reviewed and approved by the Sponsor's Coding group.

13.6 Study Management Committees

There will be no study management committees.

13.7 Record Archiving and Retention

During the pre-study and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed.

Trial documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing-out the site. The Sponsor will inform the Investigator, in writing, as to when these documents no longer need to be retained.

If the Principal Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the Sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

14 ADMINISTRATION PROCEDURES

14.1 Regulatory Approval

As required by local regulations, the Sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

14.2 Publication Policy

The Sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians patient to the consent of each individual and entity concerned, including acknowledgement of the Sponsor.

The results of this study may be published or communicated to scientific meetings by the Investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study Investigators or a Steering Committee. The Sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The Sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the Sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or authors' institution) after receipt of the proposed publication by the Sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the Sponsor's request for delay to the proposed publication should the Sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

14.3 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and contents of clinical study reports. A final CSR will be prepared where any patient has signed informed consent, regardless of whether the trial is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

14.4 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included patient, based on the calculated costs of performing the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly.

14.5 Insurance, Indemnity and Compensation

The Sponsor will provide Product Liability insurance for all patients included in the clinical study. Where required, a hospital specific indemnity agreement will be used.

15 PROTOCOL AMENDMENTS

In the event that an amendment to this protocol is required (see section 5.1), it will be classified into one of the following three categories:

- ***Non-Substantial Amendments*** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs/IRBs or CA for information purposes.
- ***Substantial Amendments*** are those considered 'substantial' to the conduct of the clinical trial where they are likely to have a significant impact on:
  - the safety or physical or mental integrity of the patients;
  - the scientific value of the trial;
  - the conduct or management of the trial; or
  - the quality or safety of the IMP used in the trial.

  Substantial amendments must be notified to the IECs/IRBs and CA. Prior to implementation, documented approval must be received from the IECs/IRBs. In the case of the CA in the European Union (EU) member states, approval or 'favourable opinion' can be assumed if the CA has raised no grounds for nonacceptance during an allocated time period (to be confirmed with the Sponsor's Regulatory Affairs (RA) representative) following acknowledgment of receipt of a valid application to make a substantial amendment.
- ***Urgent Amendments*** are those that require urgent safety measures to protect the trial patients from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent IECs/IRBs and CA notification, forthwith.

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