Clinical Study Protocol	
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A Multi-centre, Single-arm, Prospective, Interventional Study to Assess Efficacy and Safety of Neoadjuvant Hormone Therapy using Zoladex (Goserelin) and Casodex (Bicalutamide) in Patients with Advanced Prostate Cancer Undergoing Radical Prostatectomy (NARNIA)

Sponsor:

AstraZeneca Investment (China) Co. Ltd, 199 Liangjing Road, Pudong New District, Shanghai, China, 201203

VERSION HISTORY

Version 1.0, 17 Oct 2017
Version 2.0, 9 Jan 2018
Version 3.0, 7 Jun 2018
Version 4.0, 18 Dec 2019
Version 5.0, 21 Apr 2021

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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PROTOCOL SYNOPSIS

A Multi-centre, Single-arm, Prospective, Interventional Study to Assess Efficacy and Safety of Neoadjuvant Hormone Therapy using Zoladex (Goserelin) and Casodex (Bicalutamide) in Patients with Advanced Prostate Cancer Undergoing Radical Prostatectomy (NARNIA)

National Co-ordinating Investigator

- Professor Liqun Zhou, Peking University First Hospital, Beijing, China
- Professor Xin Gao, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Study site(s) and number of subjects planned

- Study sites number: 15 sites
- Number of subjects planned: 104 subjects

Study period	Timeline
Estimated date of first subject enrolled	Q1 . 2021
Estimated date of last subject in	Q4 . 2021
Estimated date of last subject last visit (LSLV)	Q3. 2022
Estimated date of database lock for whole study	Q4. 2022
Estimated date of CSR	Q1. 2023

Study design

This is a multi-centre, single-arm and prospective study to explore the efficacy and safety of neoadjuvant hormone therapy (NHT) using Zoladex (Goserelin) and Casodex (Bicalutamide) in subjects with advanced prostate cancer undergoing radical prostatectomy (RP). A total of 104 subjects diagnosed with unresectable and locally advanced prostate cancer according to the criteria will be enrolled in the study. The eligible subjects will receive Casodex 50 mg orally per day in combination with Zoladex 10.8 mg implant subcutaneously per 12 weeks for 24 weeks. The subjects will undergo a RP [RALP (robot-assisted laparoscopic prostatectomy),

laparoscopic RP or RRP (radical retropubic prostatectomy)] plus extended pelvic lymph node dissection (ePLND) thereafter if the primary tumour is assessed as resectable. Subjects will be prescribed post-surgical treatment such as continuous androgen deprivation therapy (ADT) and metastasis-directed therapy upon investigator's discretion and be followed-up for up to 3 months to evaluate the postoperative complications and the decrease of PSA.

Objectives

Primary Objective:	**Outcome Measure:**
To evaluate the efficacy of neoadjuvant hormonal therapy in the subjects with locally advanced prostate cancer through the rate of radical resection following neoadjuvant hormonal therapy (NHT)	Actual radical prostatectomy rate

Secondary Objectives:	**Outcome Measures:**
To investigate the efficacy of NHT before RP in subjects with locally advanced prostate cancer by assessment of PSA, percentage of positive surgical margin for primary tumour, incidence of seminal vesicle invasion and involvement of pelvic lymph nodes	The mean PSA at the end of NHT and PSA change from baseline
	Percentage of positive surgical margin for primary tumour (A positive surgical margin is defined as the presence of cancer at the inked margin of resection in an RP specimen)
	Incidence of seminal vesicle invasion and involvement of pelvic lymph nodes
	Pathological downstaging rate
	Rate of post surgical PSA decreased to less than 0.1ng/ml
To observe surgical-related variables and complications	Operative duration, intraoperative estimated blood loss, duration of indwelling catheterization, complications, time to continence and urinary continence rate at 12 weeks, potent rates in erectile function at 12 weeks after surgery
To evaluate the safety of NHT using goserelin and bicalutamide	AEs/SAEs

Exploratory Objective:	**Outcome Measure:**
Occurrence of homologous recombination repair gene mutation (HRRm) in the patients with locally advanced prostate cancer	Incidence of tumor tissue and germline homologous recombination repair gene mutation

Target treatment subject population

Subjects who are diagnosed with unresectable and locally advanced prostate cancer according to the criteria at clinical stage of T3 and T4 are the target population of this study.

(Definition of resectability: clear lateral border of prostate in digital rectal examination, and clear bladder neck with no invasion in radiological examination or cystoscopy, no invasion of urethra or external sphincter at the apex of prostate; non-resectable will be considered if the above definition is not met)

Planned duration of treatment

The treatment duration of study will be 24 weeks and the follow-up period will be 3 months.

The eligible subjects will receive Casodex 50 mg orally per day in combination with Zoladex 10.8 mg implant subcutaneously as neoadjuvant therapy per 12 weeks for up to 24 weeks. Then the subjects will receive radical prostatectomy if the subjects are assessed as having a resectable primary tumour. Subjects will be followed-up for up to 3 months after RP.. The reason for failure to operate will be collected for the subjects who actually can not receive radical prostatectomy following NHT.

Investigational product, dosage and mode of administration

Investigational products are Zoladex® (goserelin acetate implant) 10.8mg and Casodex® (bicalutamide) 50 mg.

- Zoladex® (goserelin acetate implant) 10.8 mg should be administered subcutaneously every 12 weeks into anterior abdominal wall below the navel line.
- Casodex® (bicalutamide) 50 mg should be taken orally once per day.

Statistical methods

The primary endpoint is the actual radical prostatectomy rate. An approximate sample size of 104 subjects provides a precision of 6.1% based on the bilateral 95% confidence interval (CI) for the resectability rate of 90% assuming a dropout rate of 10% (half width of 95% CI).

Data will be summarized using descriptive statistics as appropriate. Continuous variables will be summarised by the number of observations (n), mean (or geometric mean as appropriate), standard deviation (SD), median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. The 95% CI will be provided when appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AR	Androgen Receptor
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CAB	Complete Androgen Blockage
CI	Confidence Interval
CK	Creatine Kinase
CRF	Case Report Form
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DILI	Drug Induced Liver Injury
DMP	Data Management Plan
DNA	Deoxyribonucleic Acid
DRE	Digital Rectal Examination
EC	Ethics Committee, synonymous to Institutional Review Board (IRB)
ECG	Electrocardiogram
EDC	Electronic Data Capture
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
ePLND	Extended Pelvic Lymph Node Dissection
FAS	Full Analysis Set
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HRR	Homologous recombination repair
HRRm	Homologous recombination repair mutation
g-HRRm	Germline homologous recombination repair mutation
t-HRRm	Tumor tissue homologous recombination repair mutation
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
LHRH	Luteinizing Hormone-releasing Hormone
IMP	Investigational Medicinal Product
IP	Investigational Product
LSLV	Last Subject Last Visit
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NHT	Neoadjuvant Hormone Therapy
OS	Overall Survival
PFS	Progression Free Survival
PHL	Potential Hy's Law
PI	Principal Investigator
PSA	Prostate Specific Antigen
RALP	Robot-assisted Laparoscopic Prostatectomy
RP	Radical Prostatectomy
RPAS	RP Analysis Set
RRP	Radical Retropubic Prostatectomy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

Abbreviation or special term	Explanation
TBL	Total Bilirubin
ULN	Upper Limit of Normal

1 INTRODUCTION

1.1 Background and rationale for conducting this study

In China, about 30% patients with new prostate cancer have locally advanced prostate cancer [错误!未找到引用源。]. No distant metastasis has occurred yet in the patients with locally advanced prostate cancer and there remains the possibility of clinical cure, however, the response is poor to simple radical prostatectomy and the clinical cure rate is lower than 25% [2-5]. Therefore, more effective therapeutic regimen needs to be explored, as to improve the clinical cure rate in this portion of patients.

The clinical neoadjuvant hormonal therapy (NHT) for local prostate cancer includes androgen deprivation therapy prior to radiotherapy or surgery, usually using the therapeutic regimen of luteinizing hormone releasing hormone agonist alone or combined with anti-androgens. The rational for this approach is based on the assumption that NHT will reduce both the tumour and normal prostatic tissue volume, and induce cancer regression by the mechanism of apoptosis [6].

A series of clinical trials on neoadjuvant hormonal therapy since the early 1990s have demonstrated that NHT could reduce the positive rate of surgical margin after radical prostatectomy and down-stage the tumor, however, these studies are usually small and mainly enroll the patients with low risks or local prostate cancer, and are unable to show a more significant survival benefit in the patients with locally advanced prostate cancer receiving NHT versus those not receiving the treatment. Therefore, neoadjuvant hormonal therapy has not been recommended as the standard of care in the guideline for the patients with locally advanced prostate cancer before radical prostatectomy [7-13]. Some latest studies on neoadjuvant hormonal therapy have shown that 6-month neoadjuvant hormonal therapy prior to radical prostatectomy could better control local lesions and more effectively reduce the positive rate of surgical margin and PSA recurrence rate [14-17]. At the same time, the radiological study has also demonstrated a better efficacy of 6-month NHT than 1- or 3-month therapy [18].

Homologous recombination repair mutation (HRRm) is one common gene mutation in prostate cancer, including germline mutation and somatic cell line mutation. It has been shown in the study that HRRm was related with high-grade prostate cancer, and the prognosis was poor in the patients with prostate cancer with HRRm [19-20]. It has been shown in one small study that the incidence of germline HRRm was about 8.7% in locally advanced prostate cancer in China, however, there was lack of related study data on the incidence of tumor tissue HRRm [21].

This study is proposed primarily to observe the efficacy and safety of 24-week NHT (Zoladex and Casodex) in patients with locally advanced or oligometastatic prostate cancer. Patients will be followed up for three months after RP following NHT, as to evaluate surgery associated complications and the rate of subjects with postoperative PSA decrease to <0.1ng/ml. At the

same time, the occurrence of HRR mutation will also be explored in Chinese patients with locally advanced prostate cancer in this study.

1.2 Rationale for study design and doses

The purpose of this study is to assess the efficacy and safety of Casodex 50 mg daily in combination with Zoladex 10.8 mg implant subcutaneously every 12-weeks for 24 weeks as neoadjuvant hormonal treatment in patients with locally advanced prostate cancer.

A single-arm, prospective study is designed to enrol 104 with locally advanced prostate cancer. NHT may downstage the primary tumour and improve the surgical margin status and resectability rate of the primary tumour. The surgical efficacy and complications will be followed up for three months after RP following NHT.

Subjects will receive 24-weeks of treatment with Casodex 50 mg and Zoladex 10.8 mg implant, which have been launched in China.

1.3 Benefit/risk and ethical assessment

Casodex 50 mg daily in combination with Zoladex 3.6 mg or 10.8 mg implant are standard therapy as CAB in subjects with advanced prostate cancer. Subjects with neoadjuvant hormonal therapy are anticipated to improve the resectability of the primary tumour and reduce the proportion of positive surgical margins. Those improvements may providelonger survival benefit. The toxicities of Casodex and Zoladex are well understood and well manageable.

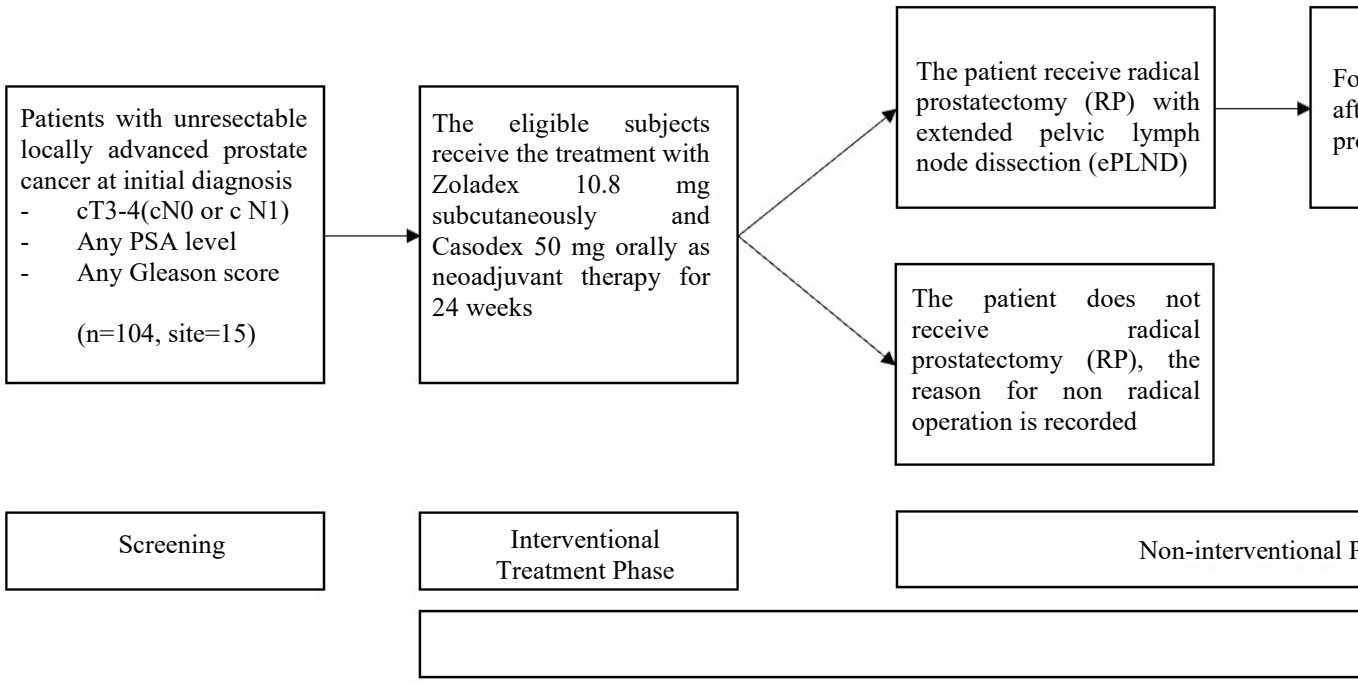
1.4 Study design

This is a multi-centre, single-arm and prospective study to explore the efficacy and safety of neoadjuvant hormone therapy (NHT) for advanced prostate cancer patients undergoing radical prostatectomy (RP). A total of 104 subjects with locally advanced prostate cancer at clinical stage of T3 and T4 (N0 or N1) will be enrolled at almost 15 centres in China.

The eligible subjects will receive Casodex 50 mg orally per day in combination with Zoladex 10.8 mg implant subcutaneously every 12 weeks as neoadjuvant therapy for 24 weeks, and then will be assessed for resectability of the primary tumour. The subjects will undergo a RP [RALP (robot-assisted laparoscopic prostatectomy), laparoscopic RP or RRP (radical retropubic prostatectomy)] plus ePLND thereafter if the primary tumour is assessed as resectable. Surgical margin status and involvement of pelvic lymph nodes will be evaluated. Subjects will be prescribed post-surgical treatment such as continuous ADT and metastasis-directed therapy upon investigator’s discretion and be followed-up for up to 3 months. The reason for failure to operate will be collected for the patients who actually can not receive radical prostatectomy following NHT.

The subjects will return for all regular clinical visits and perform all scheduled assessments until the end of study.

Figure 1 Study flow chart



Definition of resectability: clear lateral border of prostate in digital rectal examination, and clear bladder neck with n
in radiological examination or cystoscopy, no invasion of urethra or external sphincter at the apex of prostate

2 STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To evaluate the efficacy of neoadjuvant hormonal therapy in the subjects with locally advanced prostate cancer through the rate of radical resection following neoadjuvant hormonal therapy (NHT)	Actual radical prostatectomy rate

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To investigate the efficacy of NHT before RP in subjects with locally advanced prostate cancer by assessment of PSA, percentage of positive surgical margin for primary tumour, incidence of seminal vesicle invasion and involvement of pelvic lymph nodes	The mean PSA-at the end of NHT and PSA change from baseline
	Percentage of positive surgical margin for primary tumour (A positive surgical margin is defined as the presence of cancer at the inked margin of resection in an RP specimen)
	Incidence of seminal vesicle invasion and involvement of pelvic lymph nodes
	Pathological downstaging rate
	Rate of subjects with post-surgical PSA decreased to less than 0.1 ng/mL
To observe surgical-related variables and complications	Operative duration, intraoperative estimated blood loss, duration of indwelling catheterization, complications, time to continence and urinary continence rate at 12 weeks, potent rates in erectile function at 12 weeks after surgery
To evaluate the safety of NHT using goserelin and bicalutamide	AEs/SAEs

2.3 Exploratory objective

Exploratory Objective:	Outcome Measure:
Occurrence of homologous recombination repair gene mutation (HRRm) in the patients with locally advanced prostate cancer	Incidence of postoperative tumor tissue and germline homologous recombination repair gene mutation

3 SUBJECT SELECTION, ENROLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study, subjects should fulfil the following criteria:

1. Provision of informed consent prior to any study procedures
2. Male subjects
3. Age between 18 and 80 (including 18 and 80)
4. ECOG performance status 0-1
5. Histologic confirmation of prostate adenocarcinoma
6. Documented evidence of clinical stage T3 and T4 (N0 or N1)
7. Not meeting the criteria on resectability. Resectability is defined as clear lateral border of prostate in digital rectal examination, and clear bladder neck with no invasion in radiological examination or cystoscopy, no invasion of urethra or external sphincter at the apex of prostate.
8. Subject has not received local therapy for the primary lesion of prostate cancer and no contraindication for radical prostatectomy
9. Male subjects must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) for the duration of the study (from the time they sign consent) and for 3 months after the last dose of study drugs to prevent pregnancy in a partner
10. Subjects who are blood donors should not donate blood during the study and for 3 months following their last dose of study drugs
11. Subjects are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

3.2 Exclusion criteria

Subjects should not be enrolled in the study if any of the following exclusion criteria are fulfilled:

1. Staff involved in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

2. Previous enrolment in the present study

3. Participation in another clinical study with an investigational product (IP) during the last one month

4. Previous treatment with surgical castration or chemotherapy

5. Previous treatment with PARP inhibitor

6. Subjects with a known hypersensitivity to Zoladex® (goserelin acetate implant) / Casodex® (bicalutamide) or any of the excipients of the products

7. Psychiatric or medical conditions which, in the opinion of the investigator, would not allow the subject to undergo the proposed treatments safely

8. Any laboratory abnormalities, which in the opinion of the investigator（especially for subjects with moderate to severe hepatic impairment）, may put the subject at risk if participating in the study

9. Persistent toxicities (>CTCAE grade 2) caused by previous cancer therapy, excluding alopecia

10. Subjects with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids

11. Immunocompromised subjects, e.g., subjects who are known to be serologically positive for human immunodeficiency virus (HIV)

12. Unwilling or unable to comply with protocol requirements and scheduled visits

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

3.3 Subject enrolment

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject or their guardian/legal representative before any study specific procedures are performed

2. Assign potential subject a unique enrolment number

3. Determine subject eligibility. See Section 3.1&3.2

4. Enrol and treat eligible subject

If a subject withdraws from participation in the study, then his enrolment code cannot be reused.

3.4 Procedures for handling incorrectly enrolled subjects

Where a subject does not meet all the eligibility criteria but is incorrectly enrolled and started on treatment, the Investigator should inform the AstraZeneca study team immediately, and a discussion should occur between the AstraZeneca study team and the investigator regarding whether the subject need to withdraw from the study. The AstraZeneca study team must ensure all decisions are appropriately documented.

3.5 Restrictions

Subjects must abstain from donating blood/plasma from the time of informed consent and for 90 days after the last dose of the IP.

Subjects should be willing to use barrier methods of contraception during the study and for 30 days after study, unless their partners are post-menopausal, surgically sterile or are using accepted contraceptive methods.

3.6 Discontinuation of investigational product

Subjects may be discontinued from IP in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the study protocol

Patients can discontinue the investigational product at any time, without any damage to further treatment. For the patients who determine to discontinue the investigational product, the reason for the discontinuation and the occurrence of any adverse event (AE) should be always inquired. At the same time, investigators can judge if the patient is not suitable to receive the IP based on the condition, and collect the reason for the discontinuation. If the dose of Zoladex (Goserellin acetate implant) is delayed by more than 7 days during on-treatment period, early termination of study treatment will be considered. If Zoladex is permanently discontinued, Casodex should be permanently discontinued. Adverse events will be followed up (see Section 6), and patients should return all the unused investigational product.

3.7 Discontinuation/completion of the study

3.7.1 Screen failures

Screening failures are subjects who do not fulfil the eligibility criteria for the study, and therefore are not allowed to be enrolled.

3.7.2 Withdrawal of the informed consent

Subjects are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment. A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. If a subject withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn subjects will not be replaced.

3.7.3 Termination of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF (case report Form). All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

3.7.4 Completion of the study

For subjects who received RP, it will be considered as completion of the study if the subjects completed the 3 months post-surgical follow-up period.If the subjects who actually can not receive radical prostatectomy within 30 days after 24 weeks neoadjuvant therapy, it will be considered as completion of the study and reason for failure to operate will be collected.

4 STUDY PLAN AND TIMING OF PROCEDURES

4.1 Study schedule

Visit	**1**	**2**	**3**	**4**	**5[e]**	**6**	**7**	**8[g]**	**For details see Protocol Section**
Day	-28 to -1	1	85	169/End of treatment	EOT+30	RP+30	RP+90	Study completion/discontinuation	
Visit window	-	±5d	±5d	±5d		±5d	±5d	±5d	
Written informed consent	X								4.2
Demographics	X								4.2
Physical examination	X	X[a]							4.2
Medical/surgical history	X								4.2
Inclusion/exclusion criteria	X								4.2
ECOG performance status	X	X[a]	X	X	X[a]		X	X	4.2, 4.3 & 4.4
Vital signs, body weight	X	X[a]	X	X	X[a]		X	X	4.2
ECG	X	X[a]			X[a]				4.2
Imaging (CT or MRI)	X					X (clinically indicated)	X (clinically indicated)	X (clinically indicated)	4.2, 4.3 & 4.4
Bone scan	X								4.2, 4.3 & 4.4
Gleason score	X				X				4.2 & 4.4
Zoladex and Casodex treatment		X[c]	X[c]						4.3
RP evaluation				X					4.3
RP					X				4.4
Assessment after radical prostatectomy plus ePLND					X				4.4
ADT after RP						X[b]	X[b]	X[b]	4.4

Visit	**1**	**2**	**3**	**4**	**5[e]**	**6**	**7**	**8[g]**	**For details see Protocol Section**
Day	-28 to -1	1	85	169/End of treatment	EOT+30	RP+30	RP+90	Study completion/discontinuation	
Visit window	-	±5d	±5d	±5d		±5d	±5d	±5d	
Concomitant medication	X	X	X	X	X	X	X	X	4.2, 4.3 & 4.4
Adverse event	X	X	X	X	X[d]	X[d]	X[d]	X[d]	4.3 & 4.4
Haematology and clinical chemistry	X	X[a]	X	X		X	X	X	4.2, 4.3 & 4.4
Blood germline forHRRm collected				X(all patients)					4.3
Tumor tissue for HRRm collected					X[h]				4.4
Urinalysis	X	X[a]							4.2
Serum testosterone level	X	X[a]	X	X		X	X	X	4.2, 4.3 & 4.4
Serum PSA level	X	X[a]	X	X		X	X	X	4.2, 4.3 & 4.4

a. If assessed within 7 days before enrolment and meets the stated eligibility criteria (if applicable), it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.
b. The treatment will be based on investigator's discretion
c. Casodex will be administrated till Week 24
d. AEs will be actively collected from ICF to 12 weeks after last dose of Zoladex
e. Radical prostatectomy should be performed within 30 days after end of NHT. The visit will be ended for the patients without radical operation following NHT after collection of the reason for failure to receive an operation.
f. The visit will be completed after follow-up for three months following radical operation
g. As withdrawal from the study is needed as required by the patient or judged by the investigator, the visit is ended prematurely. If relevant information has been collected 7 days prior to premature end of the visit, it does not need to be re-collected at the premature end of the visit, unless a possible significant change is considered by the investigator.
h. The tumor tissue for HRRm testing will be sent out to central lab within RP+30days

4.2 Enrolment/screening period

Procedures will be performed according to the Study Plan. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or procedures.

At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled in the study. Screening and pre-treatment tests will be performed within 28 days preceding Day 1 (defined as the day of first dose of study drug). Results of standard of care tests performed prior to obtaining informed consent and within 28 days prior to study entry may be used; such tests do not need to be repeated for screening.

The study procedures carried out during this period include: demographics, physical examination, medical/surgical history, ECOG performance status, vital signs, body weight, ECG, Imaging (CT or MRI), bone scan, Gleason score, concomitant medication, haematology and clinical chemistry, urinalysis, serum testosterone level and PSA level. Results must be judged and confirmed by the investigator prior to study drug administration on Day 1.

4.3 Treatment period

Descriptions of the procedures for this period are included in the Study Plan with exceptions of the following specific requirements for the treatment period:

All visits must occur within ± 5 days starting at visit 2 from the scheduled date. All assessments will be performed on the day of the specified visit unless a time window is specified.

ECOG performance status and weight will be performed at Day 1, Day 85, or Day 169/at end of treatment visit.

Haematology and Serum chemistry will be tested at Day 1, Day 85, or Day 169/at end of treatment visit. Additional monitoring for haematology and serum chemistry will be provided as clinically indicated.

Serum PSA level and testosterone level will be collected at Day 1, Day 85 or Day 169/at end of treatment visit.

Assessment of subject's eligibility for radical prostatectomy will be performed in all enrolled subjects by investigators at Day 169/at end of treatment visit as well as blood sample for germline HRR mutation testing of all enrolled subjects will be collected.If scheduled study assessments cannot be obtained because of a holiday, these assessments should be obtained at the soonest following date, unless the soonest following date is not more than 2 days away from the evaluation time of other planned studies.

If the information as the ECOG performance status, haematology, serum chemistry, serum PSA, testosterone, concomitant medications has been collected within one week prior to the end of treatment visit, it will no more be collected, unless it is considered by the investigator that relevant information will be significantly changed in a short period.

Investigators can suggest patients to take regular serum transaminase test in the outpatient department of hospital for the first four months of treatment with Casodex and then periodically, followed clinical practice or as clinical indicated. Management of abnormal results of serum transaminase that causally related to Casodex please follow the guidance in Section 6.10.

If the dose of Zoladex (Goserellin acetate implant) is delayed by more than 7 days during on-treatment period, early termination of study treatment will be considered. If Zoladex is permanently discontinued, Casodex should be permanently discontinued.

4.4 Surgery and Post-surgical follow-up period

The ECOG performance status，vital signs, body weight，ECG，gleason score，RP，assessment after radical prostatectomy plus ePLND，adverse event，tumor tissue HRRm test will be collected on V5（EOT+30days）. The tumor tissue for HRRm testing will be sent out to central lab within RP+30days.

Radical prostatectomy should be performed for eligible subjects within 30 days after Day 169 /the end of treatment visit. The reason for failure to receive an operation will be collected for the patients without radical operation and a safety follow-up visit will be performed (12 weeks after the last dose of zoladex)

The tumor tissue for HRRm testing will be collected and sent out to central lab within 30 days after RP. All subjects receiving radical operation following NHT will be subject to evaluation of surgery related parameters as well as tumor tissue HRR mutation test after the operation. If scheduled study assessments cannot be obtained because of a holiday, these assessments should be obtained at the soonest following date, unless the soonest following date is not more than 2 days away from the evaluation time of other planned studies.

Descriptions of the procedures for this period are included in the Study Plan with exceptions of the following specific requirements for the follow-up period:

All visits must occur within ± 5 days from the scheduled date starting at visit 5, unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified.

ECOG performance status will be performed during post-surgical follow-up period, or at the study completion/discontinuation visit.

Haematology and Serum chemistry will be tested during post-surgical follow-up period（in RP+30 and RP+90）.

Serum PSA level and testosterone level will be analysed during post-surgical follow-up period, or at the study completion/discontinuation visit..

The visit will be terminated on,RP+90 days, the serum PSA level and testosterone as well as surgery associated complications will be collected.

Premature end of follow-up is needed as required by the patient or judged by investigator during follow-up, the ECOG performance status, hematology, serum chemistry, serum PSA, testosterone, concomitant medication and adverse drug reaction will be collected at the study completion/discontinuation visit.

If scheduled study assessments cannot be obtained because of a holiday, these assessments should be obtained at the soonest following date, unless the soonest following date is not more than 2 days away from the evaluation time of other planned studies.

5 STUDY ASSESSMENTS

The Electronic Data Capture (EDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA) and Good Clinical Practice (GCP) requirements. The investigator will sign the completed eCRFs.

5.1 Efficacy assessments

5.1.1 Actual radical prostatectomy rate

Actual radical prostatectomy rate is defined as the rate of the subjects who perform radical prostatectomy after NHT

5.1.2 PSA test

Prostate-Specific Antigen (PSA) will be tested in local laboratory at each site.

PSA values at baseline and at each visit during the treatment and follow-up phase, up to and including the study treatment discontinued visit will be reported for each subject.

Post-surgical PSA decreased to less than 0.1ng/ml is defined as serum PSA < 0.1 ng/ml during post-surgical follow-up period, or at termination visit

5.1.3 Tumor pathological features

Tumor pathological features will be evaluated in accordance with the postoperative pathology report issued by the department of Pathology at each study site.

Percentage of positive surgical margin of primary tumor is defined as the percentage of subjects with tumor at the margin resected in the postoperative pathological RP specimen.

Incidence of seminal vesicle invasion and involvement of pelvic lymph node is defined as the percentage of subjects with seminal vesicle invasion and those with unilateral or bilateral pelvic lymph node metastasis in the postoperative pathology.

Percentage of pathological down-stage is defined as the percentage of subjects with decreased pathological stage post operation than the preoperative clinical stage.

5.1.4 Surgical variables and complications

The main outcomes of interest are present in below to evaluate the local therapy (RP) of primary tumour. [22]

- Operative Duration is defined as the time (mins) from incision to finishing suturing.
- Intraoperative Estimated Blood Loss will be calculate using haematocrit parameters collected during the operation
- Duration of Indwelling Catheterization (Days) is defined as days from the start of surgery to removal of catheter. Institution/hospital local Urinary Catheter Indwelling and/or Removal Protocol will be applicable for each individual site.
- Complications. Percentage of subjects who experience complications and percentage of complication needing intervention in subjects who receive RP will be calculated.
- Urine function will be measured by dichotomous outcomes (continence or incontinence), where outcomes are defined as primarily the use of pads or absence of leakage. Time to Continence (Days) and urinary continence rate at 12 weeks after surgery will be reported.
- Erectile function will be measured by dichotomous outcomes (potent or impotent). Outcome results will be primarily determined by a single question will ask patients if they experience erections sufficiently firm for sexual intercourse. Potent rates in erectile function at 12 weeks after surgery will be calculated.

5.1.5 Exploratory endpoint

Occurrence of homologous recombination repair mutation (HRRm) will be explored in the patients with locally advanced prostate cancer in this study.

- All the subjects receiving surgical treatment will receive germline and tumor tissue gene test after surgery
- The gene test will be performed at the central laboratory in this study, the genes to be tested will include at least 15 homologous recombination repair related genes
- The 15 homologous recombination repair related genes include BRCA1, BRCA2, ATM, PALB2, CDK12, RAD54L, RAD51B, RAD51C, RAD51D, FANCL, CHEK1, CHEK2, PPP2R2A, BRIP1 and BARD1
- Percentage of subjects with harmful mutation of germline and tumor tissue HRR will be calculated respectively, and the rate of each harmful mutation will be recorded

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Section 4).

Additional safety monitoring may be performed and investigator can suggest patients to take additional laboratory tests in the outpatient department if clinical indicated. The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at the investigator site. Sample tubes and volume may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 1 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatase (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Creatine kinase (CK)

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

5.2.2 Physical examination

A complete physical examination will be performed and include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, respiratory, cardiovascular, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

A physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen.

5.2.3 ECG

Twelve-lead electrocardiograms (ECGs) are required to be performed as scheduled. ECGs will be reviewed by the investigator to determine if abnormality is clinically meaningful. For information on how AEs based on abnormality of ECGs should be recorded and reported, see Section 6.4.

5.2.4 Vital signs

Vital signs will include measurements of body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure and be performed as scheduled.

5.2.4.1 Pulse and blood pressure

The subject should be seated for at least 5 minutes before the measurement of pulse, systolic and diastolic blood pressure.

5.2.4.2 Body temperature

There are various types of medical thermometers, as well as sites used for measurement of body temperature, including: in in the anus (rectum/rectal), in the mouth (oral temperature), under the arm (axillary temperature), in the ear (tympanic temperature). Those measurements of body temperature are acceptable.

5.2.5 Other safety assessments

Eastern Cooperative Oncology Group (ECOG) performance status scale will be used to evaluate the subject's general well-being and activities of daily life by investigator as schedule.

The following criterial are applied:

Grade 0: Fully active, able to carry on all pre-disease performance without restriction.

Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work

Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours

Grade 3: Capable of only limited self-care, confined to a bed or chair > 50% of waking hours

Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

Grade 5: Dead

6 SAFETY REPORTING AND MEDICAL MANAGEMENT

The PI is responsible for ensuring that all staff involved in the study are familiar with the contents of this section.

6.1 Definition of adverse events

An adverse event 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.

Radical prostatectomy is the expected endpoint in this study and does not belong to adverse event.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix A to the Clinical Study Protocol.

Adverse Events (AEs) for malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual

event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is not the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

6.3 Definitions of adverse drug reaction

An Adverse Drug Reaction (ADR) is an Adverse Event suspected to be causally related to the Investigational products.

An ADR is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure

6.4 Recording of adverse events

6.4.1 Time period for collection of adverse events

Adverse Events will be actively collected and recorded from the time of informed consent up to 12 weeks after the last dose of Zoladex.

After the period, there is no obligation to actively report information on new AEs or SAEs occurring in study patients. If the investigator learns of any SAE, including a death, at any time after the period, he/she considers the event to be reasonably related to the study treatment or study participation, the investigator may notify AZ. Investigators will be encouraged to spontaneously report AZ products related AEs to AZ.

6.4.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for medical needs, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.4.3 Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date and time (if applicable) when the AE started and stopped
- max CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization (if applicable)
- Date of discharge (if applicable)
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Autopsy performed (yes or no; if yes provide report) (if applicable)
- Causality assessment in relation to Study procedure(s)
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.4.4 Causality collection

The Investigator will assess causal relationship between IP and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.4.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded appropriately according to the AE collection time period (section 6.4.1). When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation/interruption/dose reduction of treatment with the IP, or if the investigator believes that the abnormality should be reported as an AE.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In

the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4.7 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.4.8 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

6.4.9 Deaths

All deaths that occur during the study must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within 24 hours. The report should contain a comment regarding the co involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes .

6.5 Reporting of serious adverse events

All SAEs from the time of informed consent up to 12weeks after the last dose of Zoladex have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs. In addition, the investigator should report the SAE to China Authority according to local regulation and Local Ethics Committee (EC) according to local requirement.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

Investigators or other site personnel send relevant information by fax to the designated AstraZeneca representative.

6.6 Reporting non-serious of adverse drug reactions

All ADRs (i.e., Adverse Events suspected to be causally related to AstraZeneca Investigational Product) from the time of informed consent until 12weeks after the last dose of Zoladex should be reported to AstraZeneca.

If any non-serious ADR occurs in the course of the study, the investigator should inform the appropriate AstraZeneca representatives **within 5 calendar days** of when he or she becomes aware of it.

The designated AstraZeneca representatives should work with the investigator to ensure all necessary information is provided to AstraZeneca Patients Safety Data Entry Site within 5 calendar days of initial receipt.

Contact information of AZ Data Entry Site:

The below e-mail address should be used for the RAVE automatic SAE e-mail notifications:

AEMailboxWBDCTCS@astrazeneca.com

The following e-mail address should be used for all other clinical study case reports: AEMailboxClinicalTrialTCS@astrazeneca.com

Fax: +1 302 886 4114, back up fax: +46317763734

6.7 Overdose

For this study, any dose of Zoladex greater than 10.8mg per 12 weeks and/or Casodex 50mg per day will be considered an overdose. Adverse events associated with overdose should be treated symptomatically and should be managed appropriately.

For Zoladex:

The pharmacologic properties of Zoladex and its mode of administration make accidental or intentional overdose unlikely. There is no experience of overdose from clinical trials. Animal studies indicate that no increased pharmacologic effect occurred at higher doses or more frequent administration. Subcutaneous doses of the drug as high as 1 mg/kg/day in rats and dogs did not produce any nonendocrine related sequelae; this dose is up to 250 times the estimated human daily dose based on the body surface area. If overdose occurs, it should be managed symptomatically.

For Casodex:

Long-term clinical trials have been conducted with dosages up to 200 mg of Casodex daily and these dosages have been well tolerated. A single dose of Casodex that results in symptoms of an overdose considered to be life threatening has not been established.

There is no specific antidote; treatment of an overdose should be symptomatic.

In the management of an overdose with Casodex, vomiting may be induced if the subject is alert. It should be remembered that, in this patient population, multiple drugs may have been taken.

Dialysis is not likely to be helpful since Casodex is highly protein bound and is extensively metabolized. General supportive care, including frequent monitoring of vital signs and close observation of the subject, is indicated.

If an overdose occurs, the rules follows in below:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1 or 5 calendar days** if there is an SAE associated with the overdose (See section 6.4) , within **5 calendar days** for non-serious ADR (see Section 6.6) and within 30 days for all other overdose.

6.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:.

If the pregnancy is discovered before the study subject has received any study drug.

If a pregnancy is reported, the investigator should inform the sponsor within **24 hours** of learning of the pregnancy. Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

6.8.1 Paternal exposure

Male subjects must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) for the duration of the study (from the time they sign consent) and for 3 months after the last dose of Study Drugs to prevent pregnancy in a partner.

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner.

6.9 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study centre staff or subject.

Medication error includes situations where an error

- Occurred
- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognise that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g., medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g., kept in the fridge when it should be at room temperature
- Wrong subject received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to subject (excluding IVRS/IWRS errors).

Examples of events that do not require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error

- Subject accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (See section 6.4) , within 5 calendar days for non-serious ADR (see Section 6.6) and within 30 days for all other medication errors.

6.10 Management of IP related toxicities

Laboratory abnormalities including elevated AST, ALT, bilirubin, BUN (blood urea nitrogen), and creatinine and decreased hemoglobin and white cell count have been reported in both Casodex-LHRH analogue treated and flutamide-LHRH analogue treated subjects.

Rare cases of death or hospitalization due to severe liver injury have been reported post-marketing in association with the use of Casodex. Hepatotoxicity in these reports generally occurred within the first three to four months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in approximately 1% of Casodex patients in controlled clinical trials.

Serum transaminase levels should be measured prior to starting treatment with Casodex, at regular intervals for the first four months of treatment, and periodically thereafter. If clinical symptoms or signs suggestive of liver dysfunction occur (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, “flu-like” symptoms, dark urine, jaundice, or right upper quadrant tenderness), the serum transaminases, in particular the serum ALT, should be measured immediately. If at any time a subject has jaundice, or their ALT rises above two times the upper limit of normal, Casodex should be immediately discontinued with close follow-up of liver function.

7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Zoladex® (goserelin acetate implant)	Implant 10.8 mg	AstraZeneca
Casodex® (bicalutamide)	Film-coated Tablets 50 mg	AstraZeneca

Zoladex® 10.8 mg implant is supplied as sterile and totally biodegradable D. L-lactic and glycolic acids copolymer (12.8-14.76 mg/dose) impregnated with goserelin acetate equivalent to 10.8 mg goserelin in a disposable Syringe device fitted with a 14-gauges x 36 +/- 0.5 mm siliconized hypodermic needle with protective sleeve [SafeSystem™ Syringe]. The Unit is sterile and comes in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule. Store at room temperature (do not exceed 25°C).

For Casodex® (bicalutamide) of 50 mg Tablets white, film-coated tablets (identified on one side with "CDX50" and on the reverse with the "Casodex logo") are supplied in unit dose blisters of 98 tablets per carton. The Store temperature is less than 30℃.

7.2 Dose and treatment regimens

Zoladex® 10.8 mg implant will be administered subcutaneously every 12 weeks for 24 weeks.

Casodex® in combination with Zoladex® is one 50 mg tablet once daily (morning or evening), with or without food. It is recommended that Casodex® be taken at the same time each day. Treatment with Casodex® should be started at the same time as treatment with Zoladex® and continued for 24 weeks.

Treatment after RP will be dependent on the investigator's discretion.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include the following information:

- Name of sponsor (AstraZeneca)
- Investigational product/study drug dosage form, route of administration, and quantity of dosage units

- Storage conditions
- Study code
- Enrolment code
- Directions for use
- The period of use e.g., expiry date
- For clinical study use only
- Keep out of reach of children

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the pack/bottle specifies the appropriate storage.

Zoladex® 10.8 mg implant is required to store at room temperature (do not exceed 25°C) and Casodex® (bicalutamide) of 50 mg tablets is required to store at less than 30℃ temperature.

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded.

7.6 Accountability

The IP provided for this study will be used only as directed in the study protocol.

The study personnel will account for all IP dispensed to and returned from the subject.

Study site personnel or the study monitor will account for IP received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction or return should be signed.

7.7 Concomitant and other treatments

Prohibited Medication/Class of Drug:	**Usage:**
Other LHRH agonists include, not limited to: triptorelin / leuprorelin	Not permitted to be used before RP
Other antiandrogens include, not limited to: flutamide / nilutamide	Not permitted to be used before RP

7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded.

7.8 Post study access to study treatment

If ADT after RP will be given to subjects based on investigator's discretion, either Zoladex ® 10.8 mg implant or Casodex® (bicalutamide) of 50 mg Tablets will not be provided by Astrazeneca. Zoladex® 10.8 mg implant and Casodex® (bicalutamide) of 50 mg Tablets have been available on market. It will be easy to access the medication by the subjects.

8 STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject enrolled and any subsequent amendments will be documented, with final amendments completed prior to lock of the data for the primary analysis. Analyses will be performed by AstraZeneca or its representatives.

8.2 Sample size estimate

This is a single-arm, prospective study and the primary endpoint is the actual radical prostatectomy rate. An approximate sample size of 104 subjects provides a precision of 6.1% based on the bilateral 95% confidence interval (CI) for the resectability rate of 90% assuming a dropout rate of 10% (half width of 95% CI).

8.3 Definitions of analysis sets

Full analysis set (FAS)

The FAS will include all subjects who received at least one dose of study treatment, irrespective of whether some of these subjects may have discontinued treatment prior to the trial's end.

RP analysis set (RPAS)

The RPAS is defined as a subset of FAS, which includes all FAS subjects who actually received RP within 30 days by the end of NHT, regardless of prematurely discontinued treatment.

All RP related assessments will be conducted based on RPAS except for the primary analysis, where the denominator will be number of subjects in FAS.

8.4 Outcome measures for analyses

8.4.1 Primary endpoint

Actual radical prostatectomy rate

Actual radical prostatectomy rate is defined as the rate of the subjects who perform radical prostatectomy within 30 days after end of NHT

8.4.2 Secondary endpoints

- The mean PSA at the end of NHT and PSA change from baseline

- Percentage of positive surgical margins for primary tumour
- Incidence rate of seminal vesicle invasion and involvement rate of pelvic lymph nodes
- Pathological downstaging rate
- Rate of post-surgical PSA decreased to less than 0.1ng/ml

Surgical-related variables and complications Operative Duration is defined as the time (mins) from incision to finishing suturing.

Intraoperative Estimated Blood Loss will be calculate using haematocrit parameters collected during the operation and measured as a continuous variable.

Duration of Indwelling Catheterization (Days) is defined as days from the start of surgery to removal of catheter.

Complications will be presented as the percentage of subjects who receive RP and experience complications and percentage of subjects for complication needing intervention will be calculated.

Urine function will be measured by dichotomous outcomes (continence or incontinence), which outcomes are defined as primarily the use of pads or absence of leakage. Time to Continence (Days) and urinary continence rate at 12 weeks after surgery will be reported.

Erectile function will be measured by dichotomous outcomes (potent or impotent). Outcome results will be primarily determined by a single question will ask patients if they experience erections sufficiently firm for sexual intercourse. Potent rates in erectile function at 12 weeks after surgery will be calculated.

- AEs

Definition and reporting of AEs is referred to Section 6. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Summary for AEs will be presented by System Organ Class (SOC) and Preferred Term (PT).

8.4.3 Exploratory endpoint

- Incidence of homologous recombination repair mutation in tumor tissue

  Occurrence of homologous recombination repair mutation in tumor tissue is defined as the percentage of subjects with harmful t-HRRm detected in tumor tissue gene test

- Occurrence of germline homologous recombination repair mutation

8.5 Methods for statistical analyses

8.5.1 Descriptive analyses will be utilized for all endpoints. Continuous variables will be summarised by the number of observations (n), mean (or geometric mean if appropriate), standard deviation (SD), median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. The 95% CI will be provided when appropriate. Analysis of the primary variable (s)

The number of subjects to receive radical prostatectomy after NHT will be summarised. The resectability rate will be calculated with 95% CI provided using the Clopper-Pearson method.

8.5.2 Analysis of the secondary variable(s)

- PSA levelwill be summarised by the number of person (n), mean, median, SD, minimum, and maximum at each time points.
- The resection margin status (positive), seminal vesicle invasion, involvement of pelvic lymph nodes, pathological downstaging and rate of subjects with post-surgical PSA decreased to the less than 0.1ng/ml will be summarised by frequency counts and percentages.
- Surgical variables and complications will be summarized either by the number of observations (n), mean (or geometric mean if appropriate), SD, median, quartiles (Q1 and Q3), minimum, and maximum, or by frequency counts and percentages for each category.
- All AEs, serious AEs (SAEs), drug related AEs, and AEs leading to study drug discontinuation will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and CTCAE grade.
- Treatment-emergent AEs, i.e., the AEs occurring on or after the first dosing of study drug and up to 4 weeks after discontinuation of study drug, will be included in the AE summaries.

8.5.3 Interim analysis

No interim analyses are planned.

9 STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the

investigational staff and also train them in any study specific procedures and the EDC and/or any other system(s) utilised.

The PI will ensure that appropriate training relevant to the study is given to all of these staffs, and that any new information relevant to the performance of this study is forwarded to the staffs involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the

conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.2.4 Deviation from the clinical study protocol

The Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the PI and AstraZeneca or the institutional review board (IRB) approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the subjects or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (e.g., changes to the organisation/structure of the AstraZeneca, the name/department name of the study site, the address or phone number of the study site or AstraZeneca, the job title of the Investigator, and monitors).

The Investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the subjects or for other medically compelling reason, the Investigator should prepare and submit the records explaining the reasons thereof to AstraZeneca and the head of study site, and retain a copy of the records.

The Investigator(s) may deviate from or make a change to the protocol without documented agreement between the PI and AstraZeneca or the IRB approval, only in the event of a medical emergency, e.g., it is only way to avoid an immediate hazard to the subjects. In such case, the PI must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca and the head of the study site and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca should be obtained via the head of the study site.

9.3 Study timetable and end of study

The end of the study is defined as ‘the last visit of the last subject undergoing the study’.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with Zoladex and Casodex.

9.4 Data management by AstraZeneca or Delegate

Data management will be performed by an AstraZeneca representative.

Data will be entered in the electronic data capture (EDC) system at the Investigator's site. The Investigator (or delegate) will be responsible for entering data into the EDC system and according to the Investigator Instructions Manual. The Investigator Instructions Manual will also provide the study site with data entry instructions.

Data entered in the EDC system will be immediately saved and changes tracked to provide an audit trail. When data have been entered, reviewed and edited, the Investigator will be notified to sign the CRF as per the agreed project process. A copy of the CRF will be archived at the Investigator's site.

Medical Coding will be performed using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug Dictionary.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the DMP. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, clean file will be declared..

Management of external data

The data collected through third party sources will be obtained and reconciled against study data. Data from external providers (e.g. central laboratories) will be validated as appropriate to ensure it is consistent with the clinical data.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The EC should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an EC.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the National Co-ordinating Investigator, and the PI and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to EC see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's EC are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable

regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc)
- Convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.