Study Title: HERO: A Multinational Phase 3 Randomized, Open-Label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer

NCT Number: 03085095

Document Date: Protocol Version 1 /13 January 2017
Amendment 1 / 02 January 2018
Amendment 2 / 18 January 2018
Amendment 3/ 23 October 2018

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Original Protocol (13-Jan-2017)

Amendment 1 (02-Jan-2018)

Amendment 2 (18-Jan-2018)

Amendment 3 (23-Oct-2018)

CLINICAL STUDY PROTOCOL

Study Title:	HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3201
Indication:	Advanced Prostate Cancer
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
IND Number:	118736
EudraCT Number:	2017-000160-15
Version / Effective Date:	Version 1 /13 Jan 2017
Study Medical Monitor:	PPD

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Myovant Sciences GmbH, and is provided to you in confidence as an investigator, potential investigator or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Myovant Sciences GmbH, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SPONSOR SIGNATURE PAGE

HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer

Protocol Number: MVT-601-3201

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

13 Jan 2017

Date

13 Jan 2017

Date

13 Jan 2017

Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	**Signature**
Date	**Site**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
3-M	3-month
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
$AUC_{0-\tau}$	area under the concentration-time curve from time 0 to the end of the dosing interval
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DHT	dihydrotestosterone
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation of Research and Treatment of Cancer
EOT	end of treatment
EuroQol EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Questionnaire
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HbA1c	hemoglobin A1c
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
ICH	International Conference on Harmonization
ID	identification
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat (population)
IWRS	interactive voice/web recognition system
LH	luteinizing hormone
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse-effect-level

Term	Explanation
Obs	observed
PK	pharmacokinetics
PLD	phospholipidosis
PSA	prostate-specific antigen
Q12W	once every 12 weeks
Q4W	once every 4 weeks
QD	once daily
QTc	QT interval corrected for heart rate
SHBG	sex hormone binding globulin
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States

1. PROTOCOL SYNOPSIS

Study Title	HERO: A Multinational Phase 3, Randomized, Open-label, Parallel-group Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer
Protocol Number	MVT-601-3201
Location	Multinational, including North and South America, Europe, and Asia-Pacific
Study Centers	Approximately 200 sites
Study phase	Phase 3
Target Population	Men aged 18 or older diagnosed with androgen-sensitive advanced prostate cancer who are candidates for at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer and who are not be candidates for surgical therapy. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy.
Number of Patients Planned	1125 total patients
Study Objectives	Primary: • To evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) in men with androgen-sensitive advanced prostate cancer. Secondary: • To evaluate the time course and change in serum testosterone during treatment with relugolix; • To evaluate the time course and magnitude of prostate-specific antigen (PSA) reduction during treatment with relugolix; • To evaluate testosterone recovery following discontinuation of relugolix; • To evaluate quality of life using validated patient-reported outcome instruments; • To evaluate the safety of relugolix 120 mg once daily in men with androgen-sensitive advanced prostate cancer; • To evaluate the effect of relugolix and leuprolide acetate on endocrine pharmacodynamic parameters; • To collect relugolix plasma concentration data to further evaluate relugolix population pharmacokinetics (PK) and the relationship between relugolix exposure and serum testosterone; and • To characterize the relugolix plasma PK parameters in a subset of patients from China and Japan.

	Exploratory: • To explore the overall survival of patients treated with relugolix; and • To explore the contribution of genetic variance on drug response.

Study Design

The HERO study is a phase 3 multinational randomized, open-label, parallel-group study to evaluate the safety and efficacy of relugolix in patients with androgen-sensitive advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy. Relugolix is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist that lowers testosterone by inhibiting pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Relugolix 120 mg orally once daily or leuprolide acetate depot suspension, 22.5 mg (or 11.25 mg in some Asian countries), every 3-months (3-M) by subcutaneous or intramuscular injection will be administered to patients with prostate cancer who require androgen deprivation therapy. This study will evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) for 48 weeks in patients with androgen-sensitive advanced prostate cancer.

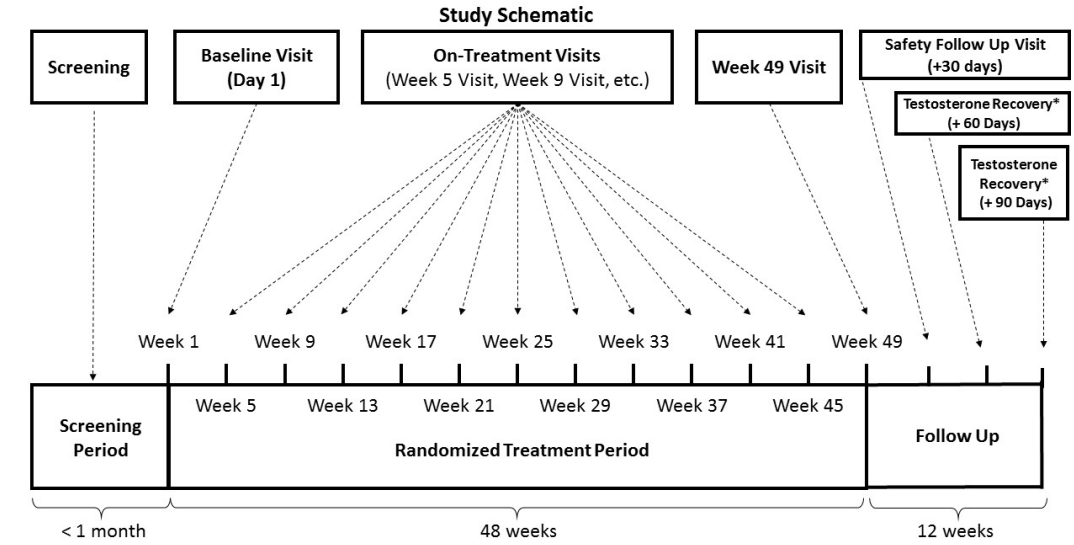
To be eligible for the study, a patient must be, in the opinion of the investigator, a candidate for at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer and must not be a candidate for surgical therapy. Eligible patients include those with evidence of biochemical relapse (rising PSA) following local primary intervention with curative intent, newly diagnosed metastatic disease (excluding metastases to the brain), and/or advanced localized disease. Patients may receive radiotherapy, cryotherapy or high frequency ultrasound no sooner than 2 months after initiation of androgen deprivation therapy. Patients may be included if they have not previously received androgen deprivation therapy for more than 12 months, and if the androgen deprivation therapy was completed at least 12 months prior to baseline. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy. Baseline serum testosterone must be ≥ 150 ng/dL (5.2 nmol/L) to be enrolled.

Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg once daily following a loading dose of 360 mg on Day 1 or leuprolide acetate 22.5 mg (or 11.25 mg in some Asian countries) 3-M depot subcutaneous or intramuscular injection, respectively, plus an antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator. Randomization will be stratified by geographic region, presence of metastatic disease, and age.

Approximately 1125 patients will be enrolled in this study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region. The study includes a Screening Period of up to 28 days, a Treatment Period of 48 weeks, and a Follow-up Period of up to 90 days. Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed. Eligible patients will receive study treatment for 48 weeks. During that time, testosterone and PSA will be assessed monthly and patient-reported outcomes (European Organisation of Research and Treatment of Cancer [EORTC] QLQ-C30, European Quality of Life 5-Dimesion 5-Level questionnaire [EuroQol EQ-5D-5L]) will be assessed approximately every 3 months during the Treatment Period and more frequently during the Follow-up Period. Additional serum endocrine evaluations will include: LH, FSH, dihydrotestosterone, and sex hormone binding globulin. Relugolix PK samples will be collected throughout the study. Full PK profiles will be determined in a subset of patients in China and Japan. Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECG), and

visual acuity tests.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (testosterone level ≤ 50 ng/dL [1.7 nmol/L]), should remain on study and may receive additional oral therapy, systemic antineoplastic, and/or radiotherapy as prescribed by the investigator.



Inclusion/Exclusion Criteria

Inclusion Criteria

All of the following inclusion criteria must have been met prior to randomization unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a male aged 18 years or older on the day of signing and dating the informed consent form;
3. Has histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate;
4. Is a candidate for, in the opinion of the investigator, at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer with one of the following clinical disease state presentations:
   a. Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, such as surgery, radiation therapy, cryotherapy, or high-frequency ultrasound and not a candidate for salvage treatment by surgery (radiotherapy, cryotherapy, or high frequency ultrasound are allowed after 2 months of androgen deprivation therapy); or
   b. Newly diagnosed androgen-sensitive metastatic disease; or
   c. Advanced localized disease not suitable for local primary surgical intervention with

curative intent (radiotherapy, cryotherapy, or high frequency ultrasound are allowed after 2 months of androgen deprivation therapy);

5. Has a serum testosterone at the Screening visit of ≥ 150 ng/dL (5.2 nmol/L);
6. Has a serum PSA concentration at the Screening visit of > 2.0 ng/mL (2.0 µg/L), or, when applicable, post radical prostatectomy of > 0.2 ng/mL (0.2 µg/L) or post radiotherapy, cryotherapy, or high frequency ultrasound > 2.0 ng/mL (2.0 µg/L) above the post interventional nadir;
7. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at initial screening and at baseline (refer to Appendix 1);
8. Is a male patient who, even if surgically sterilized (ie, status post vasectomy):
   a. Agrees to use a male condom if having sex with a woman of childbearing age or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or
   b. Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception;
9. Must agree not to donate sperm from first dose of study drug through 4 months after the last dose of study drug;
10. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

1. In the investigator's opinion, is likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating androgen deprivation therapy;
2. Previously received GnRH analog or other form of androgen deprivation therapy (estrogen or antiandrogen) for > 12 months total duration. If androgen deprivation therapy was received for ≤ 12 months total duration, then that therapy must have been completed at least 12 months prior to baseline;
3. Previous treatment for prostate cancer with a taxane-based regimen;
4. Metastases to brain per prior clinical evaluation;
5. Features of the patient's medical condition that make life expectancy due to other medical conditions of less than 5 years;
6. Scheduled for major surgery after baseline;
7. History of surgical castration;
8. Diagnosis of or treatment for another malignancy within the 2 years before baseline, or presence of another malignancy with evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection. Patients with Stage 0 or Stage 1 melanoma or superficial Stage 0 or Stage 1 bladder cancer, if curatively managed prior to screening, are not excluded. The medical monitor should be contacted for any questions regarding this

exclusion criterion;

9. Abnormal laboratory values at the Screening visit that suggest a clinically unstable underlying disease, or the following laboratory values:
   a. Serum gamma-glutamyl transferase > 2.0 x upper limit of normal (ULN);
   b. Serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 1.0 x ULN;
   c. Total bilirubin > 1.0 x ULN (unless secondary to Gilbert's syndrome or the pattern is consistent with a diagnosis of Gilbert's syndrome) or;
   d. Serum creatinine > 2.0 mg/dL;
10. Uncontrolled diabetes with hemoglobin A1c (HbA1c) > 10% or previously undiagnosed diabetes mellitus with screening HbA1c > 8% (such excluded patients may be rescreened after referral and evidence of improved control of their condition);
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (hepatitis A virus immunoglobulin M [IgM] positive), hepatitis B (hepatitis B virus surface antigen [HBsAg] positive), or hepatitis C (hepatitis C virus [HCV] antibody positive, confirmed by HCV ribonucleic acid);
12. Known human immunodeficiency virus infection;
13. Within 6 months before baseline, a history of myocardial infarction, angina, unstable symptomatic ischemic heart disease, or congestive heart failure, or any history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of Mobitz II second degree or third degree heart block without permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute); thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events); or any other significant cardiac condition (eg, pericardial effusion, restrictive cardiomyopathy). Patients with chronic stable atrial fibrillation on stable anticoagulant therapy or patients with stable cardiac rhythm controlled by a pacemaker are allowed;
14. The following ECG abnormalities are excluded:
   a. Q-wave infarction, unless identified 6 or more months before the Screening visit;
   b. QT interval corrected for heart rate (QTc) > 470 msec. If the QTc is prolonged in a patient with a pacemaker, the patient may be enrolled in the study upon discussion with the medical monitor; or
   c. Congenital long QT syndrome;
15. Uncontrolled hypertension despite appropriate medical therapy (sitting blood pressure of greater than 160 mmHg systolic and/or 100 mmHg diastolic at 2 separate measurements no more than 45 minutes apart during the Screening visit). Patients may be re-screened after referral and further management of hypertension;
16. Hypotension, as indicated by systolic blood pressure < 84 mmHg on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming upright position;
17. Bradycardia as indicated by a heart rate of < 45 beats per minute on the ECG at the Screening or Baseline Day 1 visit;

18. Treatment for prostate cancer with any investigational products within 12 months before the first dose of study drug (approved products under investigation for an alternative condition, not directly related to therapy for prostate cancer, may be allowed); 19. Treatment with an investigational product for indications other than prostate cancer within 3 months; 20. Previous treatment with relugolix in a clinical study; 21. Patient is a study site employee or is a primary family member (spouse, parent, child, or sibling) of a site employee involved in the conduct of the study; 22. Known gastrointestinal disease or procedure that could interfere with the oral absorption or tolerance of relugolix, including inability to swallow whole tablets; 23. Use of any medication listed in the prohibited medications table (see Section 5.10.1) without the appropriate washout period; 24. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation; 25. Has a prior (within 1 year of the Screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form [eCRF]); 26. Any serious medical condition that limits life expectancy to less than 5 years, or any other medical or psychiatric condition that, in opinion of investigator, would interfere with completion of treatment according to this protocol.	
Dose and Route of Administration	Test Product Relugolix 120 mg tablet strength will be available as immediate-release film-coated tablets, and 1 tablet (120 mg) will be administered once daily following an oral loading dose of 360 mg (three 120-mg tablets) on Day 1. These tablets will be presented in 45-tablet bottles and dispensed to patients every 4 weeks at scheduled study visits. All protocol-specific inclusion criteria and none of the exclusion criteria must be met and documented prior to study drug administration. Study drug will be dispensed only to eligible patients who are under the supervision of the investigator or identified subinvestigator(s). Reference Product Leuprolide acetate, 22.5 mg (or 11.25 mg in some Asian countries), 3-M depot subcutaneous or intramuscular injection will be administered per the approved dose and method of dosing in the region where the patient is enrolled. Leuprolide acetate 3-M depot injection will be administered on Day 1 (with an antiandrogen of choice, if indicated according to the investigator, for the first 4 weeks or longer), then at 12-week intervals thereafter for 48 weeks. Preparation of the depot injection should follow the instructions provided by the manufacturer.
Duration of Treatment	The duration of treatment will be 48 weeks. The last dose of leuprolide acetate 3-M depot will be administered at the Week 37 visit.

Criteria for Evaluation	The following treatment arms will be evaluated after 48 weeks of study treatment: • Arm A: Oral relugolix 120 mg once daily following a loading dose of 360 mg (three 120-mg tablets) on Day 1. • Arm B: Leuprolide acetate 3-M depot injection, 22.5 mg (or 11.25 mg in some Asian countries). <u>Primary Endpoint</u> • Sustained castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). <u>Secondary Endpoints</u> • Describe effects on serum testosterone: o Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4, prior to dosing on Week 2, and prior to dosing on Week 3; o Profound castration rate defined as the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) while on study treatment from Week 25 Day 1 through Week 49 Day 1; o Time to testosterone recovery in the first 100 patients randomized to relugolix and the first 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of leuprolide acetate 3-M depot); • Describe effects on PSA: o Proportion of patients with confirmed PSA response by Prostate Cancer Clinical Trials Working Group 3 guidelines at the Week 2 and 5 visits [Scher, 2016]; o Proportion of patients with PSA concentration < 0.2 ng/mL (0.2 µg/L) at the Week 25 visit; • Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable during the Follow-up and/or at End of Treatment visits; • Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as the EuroQol EQ-5D-5L questionnaire, at regular intervals during treatment, and as applicable during the Follow-up visits; • Incidence of adverse events; • Incidence of abnormalities in clinical laboratory data; • Endocrine marker effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for: o LH at the Week 2, Week 3, and Week 5 visits, and then every 4 weeks until the last follow-up visit; o FSH at the Week 5, Week 13, Week 25, Week 37, and Week 49 visits;

	○ Dihydrotestosterone at the Week 5, Week 13, Week 25, Week 37, and Week 49 visits; and ○ Sex hormone binding globulin at the Week 13, Week 25, and Week 49 visits; • Predose relugolix plasma concentrations; • Single and repeat-dose plasma relugolix PK parameters such as maximum plasma concentration (C_{max}), area under the concentration-time curve from time 0 to the end of the dosing interval ($AUC_{0-\tau}$), and time to maximum plasma concentration (t_{max}) in a subset of patients from China and Japan during the Day 1 visit. <u>Exploratory Endpoints</u> • Overall survival defined as time from randomization to date of death prior to data cutoff date; and • The presence of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) population defined as all randomized patients who have taken at least one dose of study treatment. Randomization will be stratified by geographic region (North and South America versus Europe versus Asia and Rest of World), presence of metastatic disease on baseline imaging (yes versus no), and age (≤ 75 years old versus > 75 years old). The 2-sided type I error rate for this study is 0.05.

Primary Efficacy Endpoint:

The primary efficacy endpoint is the sustained castration rate defined as the cumulative probability of achieving testosterone suppression to castrate levels of ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). This probability will be estimated for each treatment group using the Kaplan-Meier method with the confidence interval calculated using the exponential Greenwood formula via log-log transformation of the survival function. Patients who discontinue treatment prior to observing a testosterone level > 50 ng/dL (1.7 nmol/L) will be censored at the last testosterone assessment prior to discontinuation. Detailed censoring rules will be prespecified in the statistical analysis plan.

There are 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit:

- Evaluation Criterion 1: to determine whether the sustained castration rate for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression to castrate levels in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion.
- Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot as assessed by the cumulative probability of sustained testosterone suppression to castrate levels. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression to castrate levels between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.

The 2-sided type I error rate will be 0.05 for each individual evaluation criterion.

Secondary Efficacy Endpoints:

1. Castration rate: the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4, prior to dosing on Week 2, and prior to dosing on Week 3;
2. Profound castration rate: the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) from Week 25 through Week 49;
3. PSA response rate: proportion of patients with a ≥ 50% decrease in PSA from baseline at Week 2 and confirmed at Week 5;
4. Undetectable PSA rate: proportion of patients with PSA concentration < 0.2 ng/mL (0.2 µg/L) at the Week 25 visit;
5. Time to testosterone recovery in the first 100 relugolix-treated and first 50 leuprolide acetate-treated patients who complete 48 weeks of treatment and do not start alternative androgen deprivation therapy within 12 weeks after the last dose of relugolix or within 24 weeks following the last received injection of leuprolide acetate. Kaplan-Meier methods will be used to describe survival distributions;
6. Quality of Life: absolute values and changes from baseline in the scores of the EORTC-

QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable at the Follow-up and/or End-of-Study visits will be presented. Additionally, absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as EQ-5D-5L, at regular intervals during treatment, and as applicable during the Follow-up visits will be presented. Change from baseline will be analyzed using mixed-model repeated measures methodology.

Exploratory Endpoints:

1. Overall survival: Overall survival defined as time from randomization to date of death prior to data cutoff date. Kaplan-Meier methods will be used to describe survival distributions;
2. The effect of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or drug metabolizing enzymes and transporter proteins on the efficacy and safety of relugolix will be described in a separate statistical analysis plan.

The methods and procedures needed to maintain a study-wide 2-sided type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

Pharmacokinetics

Relugolix plasma concentrations will be summarized and described using population PK methods. Plasma PK parameters in a subset of patients from China and Japan will be determined using noncompartmental methods.

Safety

Safety assessments, including adverse events, vital signs, clinical laboratory tests, and ECGs, will be summarized for the treatment-emergent period. The treatment-emergent period is defined as the time from first dose of study drug through 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last dose of leuprolide acetate. Safety analyses will be based on all randomized patients who receive any amount of study drug (Safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher-level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive rather than inferential statistics will be used. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of baseline versus post baseline results will be produced.

An independent Data and Safety Monitoring Board will monitor all available safety data on a periodic basis. The roles and responsibilities of the Data and Safety Monitoring Board will be described in detail in a separate charter.

Sample Size

To calculate the sample size required for the primary efficacy endpoint of this study, the following assumptions have been made:

- True probabilities of sustained castration rates are 94% and 96% for relugolix and leuprolide acetate, respectively;

- 2:1 randomization ratio (relugolix:leuprolide acetate);
- Dropout rate of 15%.

For Evaluation Criterion 1, 610 patients in the relugolix group will provide approximately 90% power to rule out a fixed probability of sustained testosterone suppression of ≤ 90% at a 2-sided type I error rate of 0.05.

For Evaluation Criterion 2, with the non-inferiority margin of -10% and a 2-sided type I error rate of 0.05, a total of approximately 915 patients (610 relugolix, 305 leuprolide acetate) will yield at least 99% power in declaring the non-inferiority of relugolix compared to leuprolide acetate.

The primary analysis of the primary efficacy endpoint will be performed after at least 915 patients have had the opportunity to complete 48 weeks of study drug treatment. The evaluation criteria used for the primary efficacy endpoint assessment will be determined by regional regulatory requirements and will be prespecified in separate regional statistical analysis plans.

Up to approximately 1125 men will be randomized in order to fulfill the regulatory requirements of all participating countries. This includes approximately 90 patients from Japan, approximately 111 patients in South Korea, and approximately 200 patients from China PR.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3201

Period	**Screening Visit**	**Treatment Period Visits**														**Follow-up[a,b,c]**		
																Safety	**Testosterone Recovery**	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 9[d]**	**Wk 13[d]**	**Wk 17 and 21[d]**	**Wk 25[d]**	**Wk 29 and 33[d]**	**Wk 37[d]**	**Wk 41 and 45[d]**	**Wk 49[d,e]**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**	**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**		**±1 day**				**± 7 days**									**± 7 days**		
Informed Consent[f]	X																	
Inclusion/ Exclusion Criteria	X	X																
Study Drug Dispensation: Relugolix		X					X	X	X	X	X	X	X	X				
Study Drug Administration: Relugolix Once Daily		X	X Patients will receive a single loading dose of oral relugolix 360 mg on Day 1 in the clinic; Starting on Day 2, patients will receive oral relugolix 120 mg once daily															
Study Drug Administration: Leuprolide Acetate 3-M Depot		X							X		X		X					
Demographics	X																	
Medical History (including detailed prostate cancer history)	X	X																
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, BMI	X	X							X		X				X	X		
Height	X																	
12-lead ECG[g]	X	X					X		X		X				X	X		

Myovant Sciences GmbH 23 CONFIDENTIAL

Period	**Screening Visit**	**Treatment Period Visits**														**Follow-up[a,b,c]**		
																Safety	**Testosterone Recovery**	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 9[d]**	**Wk 13[d]**	**Wk 17 and 21[d]**	**Wk 25[d]**	**Wk 29 and 33[d]**	**Wk 37[d]**	**Wk 41 and 45[d]**	**Wk 49[d,e]**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**	**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**		**±1 day**				**± 7 days**									**± 7 days**		
ECOG Performance Assessment	X	X									X				X	X		
Complete Physical Exam and Visual Acuity[h]	X										X				X			
Symptom Based Physical Exam		X	X	X	X	X	X	X	X	X		X	X	X		X	X	X
Abdominopelvic CT or MRI and Bone Scan[i]	X																	
EuroQol EQ-5D-5L Health Questionnaire		X					X		X		X		X		X	X	X	X
EORTC-QLQ-PR25 and EORTC-QLQ-C30 Quality of Life Questionnaires		X					X		X		X		X		X	X	X	X[i]
Adverse Events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X							X		X		X		X	X		
Chemistry	X	X					X		X		X		X		X	X		
Lipid & HbA1c[k]	X										X				X	X		
PSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Testosterone/LH	X	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X	X
SHBG		X							X		X				X			X
FSH/DHT		X					X		X		X		X		X			

Myovant Sciences GmbH 24 CONFIDENTIAL

Period	**Screening Visit**	**Treatment Period Visits**														**Follow-up[a,b,c]**		
																Safety	**Testosterone Recovery**	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 9[d]**	**Wk 13[d]**	**Wk 17 and 21[d]**	**Wk 25[d]**	**Wk 29 and 33[d]**	**Wk 37[d]**	**Wk 41 and 45[d]**	**Wk 49[d,e]**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**	**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**		**±1 day**				**± 7 days**									**± 7 days**		
Blood Sample for Relugolix PK[m,n]		X[m,n]	X[m,n]	X[m,n]			X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]			
Blood Sample for DNA[o]		X																
Health Status Survey[p]															X			

Abbreviations: 3-M, 3-month; BMI, body mass index; CT, computed tomography; DHT, dihydrotestosterone; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; EuroQol EQ-5D-5L, European Quality of Life 5-Dimension 5-Level; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; LH, luteinizing hormone; MRI, magnetic resonance imaging; PK, pharmacokinetics; PSA, prostate-specific antigen; SHBG, sex hormone binding globulin

a. The study day in which the Follow-up visit occurs is not specified in the table because these visits occur relative to when the patient takes his last dose of study drug. The End of Treatment (EOT) is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.
b. May occur earlier for patients who are starting alternative androgen deprivation therapy, or do not complete 12 weeks of study treatment. Adverse events, serious adverse events, and concomitant medications should continue to be collected and recorded through 30 days after the End of Treatment. All other study procedures should be completed before the start of alternative androgen deprivation therapy.
c. Patients who have started alternative androgen deprivation therapy will not participate in the 60- and 90-day Follow-up visits. For the first 100 patients receiving relugolix and 50 patients receiving leuprolide acetate who complete 48 weeks of study drug treatment and, in the opinion of the investigator, can remain off androgen deprivation therapy for 90 days will be included in the testosterone recovery 60- and 90-day Follow-up visits.
d. For patients assigned to the relugolix treatment arm, the patient should be called 7 days before their next visit to check on compliance with their study medication.
e. If patient terminates early from study treatment, the patient should be asked to come in as soon as possible and complete this visit.
f. The informed consent form must be signed before any study-mandated procedures are performed.
g. 12-lead ECGs should be read locally by a qualified physician.
h. A complete physical examination should be performed. Visual acuity will be evaluated by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment.
i. An abdominopelvic CT or MRI and a bone scan should be performed and read locally to determine the presence of metastatic disease within 60 days prior to randomization.
j. Serious adverse events should be collected from the time the patient signs the informed consent form through 30 days after the last dose of relugolix treatment or 12 weeks and 30 days after the last injection of leuprolide acetate. Treatment-emergent adverse events are collected from the time of the first dose of study drug through 30 days after the last dose of relugolix treatment or 12 weeks and 30 days after the last injection of leuprolide acetate.

k. Blood samples must be obtained fasting; nothing to eat or drink (other than water) overnight and prior to obtaining the sample.
l. All testosterone samples obtained from Week 5 and beyond are to be collected during a ± 7-day window.
m. Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose; patients will be required to arrive at the clinic on an empty stomach (after an overnight fast or at least 2 hours after food; food should be withheld for 1 hour after dosing). Patients will be dosed in the clinic at these visits.
n. A subset of patients from China and Japan will have additional samples collected predose, and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Day 1 and Week 2 visits. A predose sample also will be collected at the Day 4 visit. Patients will be required to arrive at the clinic on an empty stomach (after an overnight fast or at least 2 hours after food; food should be withheld for 1 hour after dosing). Patients will be dosed in the clinic at these visits.
o. The blood sample for DNA should be collected at the Baseline Day 1 visit, but may be collected at any visit if it is missed at that visit.
p. During the final weeks prior to database lock, sites will be asked to contact all study participants or their immediate family regarding the current health status of previously enrolled/completed study patients.

2. INTRODUCTION

2.1. Prostate Cancer

Prostate cancer is the most prevalent form of cancer in men and the second leading cause of death due to cancer in men in the US [Greenlee, 2001] and Europe [Ferlay, 2007]. The median age of diagnosis is 70 years, and diagnosis before the age of 40 years is rare [Cersosimo, 1996]. In Japanese men, prostate cancer was the fourth leading cancer diagnosis in 2007 [Foundation for Promotion of Cancer Research, 2012]. The incidence of invasive prostate cancer increases with age; a clear increase is seen among men aged 60 years or older [Siegel, 2014].

If prostate cancer is diagnosed at a stage where it is confined to the prostate gland and immediate surroundings, it is generally treated by surgical removal of the prostate gland, or prostatectomy, or with radiation. Often, these procedures are successful in curing men of their disease. Men whose disease progresses after prostatectomy or radiation are said to have advanced prostate cancer. Advanced prostate cancer is defined as either: PSA biochemical relapse following primary surgical or radiation therapy of curative intent; newly diagnosed metastatic prostate cancer; or advanced localized disease for which immediate radiation or surgical therapy is not indicated. The cure rate following surgery, depending on the stage of the cancer, is about 70% overall and, following radiation, about 50% to 60%.

Approximately 25% to 30% of men will, therefore, progress to advanced disease, excluding those with metastatic disease at the time of diagnosis. Androgens, such as testosterone and its more potent metabolite dihydrotestosterone, are strong tumor promoters for prostate cancer [Bosland, 2014]. Through the androgen receptor, they synergistically augment the effect of other tumor promoters or carcinogens. Although prostate cancer is driven by presumed mutations in other tumor promoting pathways and/or by translocations leading to aberrant activation of the androgen receptor pathway, most early-stage prostate cancer cells remain either sensitive to or dependent upon circulating androgens. Thus, for more than 60 years, androgen deprivation therapy with surgical or medical castration has been the foundational therapy for either advanced inoperable or metastatic cancer. Increasingly, androgen deprivation therapy is used earlier as a neoadjuvant/adjuvant treatment to radiation therapy or for biochemical or clinical relapse after local therapies of curative or palliative intent. More than 80% of men with progressive or advanced disease initially respond to androgen deprivation therapy with varying degrees of tumor regression or stabilization [Kreis, 1995]. The duration and depth of response to androgen deprivation therapy is presumably dependent on the underlying tumor biology and burden. Thus, patients with metastases respond for an average of 2 years before any biochemical evidence of castration resistance occurs. By contrast, patients with biochemical-only evidence of progressive disease may respond to androgen deprivation therapy for 5 years or more [Klotz, 2015].

Currently, most patients in developed countries receive medical rather than surgical castration. GnRH (or LH-releasing hormone) agonists (ie, long-acting leuprolide acetate depot injections) are the current mainstay of medical castration, causing long-term desensitization and down regulation of the hypothalamic-pituitary gonadal axis. One disadvantage of the agonist form of GnRH is the initial stimulation of the axis lasting 1 to 3 weeks that occurs prior to desensitization. This results in a rise in LH and testosterone levels and an increase in clinical symptoms. In addition, at the time of repeat injection of GnRH agonist depot, microsurges of

LH and testosterone may occur, although the apparent incidence is low [Klotz, 2008]. The initial flare response may be managed with simultaneous antiandrogen administration, such as with bicalutamide.

Recently, GnRH antagonists, in particular degarelix, [Firmagon, 2016], have become available as an alternative form of medical castration. Degarelix, an injectable peptide, has been approved in some countries for the treatment of patients with advanced prostate cancer. As a GnRH antagonist, degarelix achieves medical castration and PSA response with no initial agonist activity within the first 1 to 2 weeks of administration, and effectively can obviate the need for concomitant antiandrogen treatment. Post-hoc analyses of degarelix trials [Tombal, 2010] suggest that it may have additional advantages regarding disease response or secondary relapse; however, such differences require confirmation in prospective studies. Because of the need for monthly depot injections, with large volumes and accompanying local reactions, the use of degarelix in clinical practice has remained low.

Relugolix, previously known as TAK-385, is a potent and highly selective oral small molecule antagonist for the human GnRH receptor. For patients, relugolix may offer the advantages conferred by a direct receptor antagonist, including a more rapid onset of action and the absence of clinical flare or worsening of symptoms from the initial rise in androgens caused by GnRH agonists, as well as having the added convenience and relative comfort of oral dosing.

2.2. Relugolix

2.2.1. Indication

Relugolix is being developed as a once daily oral medication for the treatment of advanced prostate cancer. The proposed dose of relugolix is 120 mg administered orally once daily following a loading dose of 360 mg (three 120-mg tablets) on Day 1.

2.2.2. Pharmacology

Relugolix is an orally-active, potent, highly-selective, high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes the human GnRH receptors present on the gonadotrophin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in testosterone in men and estradiol and progesterone levels in women. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 μg·hr/mL, which is ~51 times higher than the estimated exposure (area under the concentration-time curve [AUC]) in men receiving 120 mg once daily (0.469 μg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 μg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥ 100 mg/kg (estimated C_{max} of 4.0 μg/mL), but did not prolong the QT interval in a human Thorough QT study at doses up to 360 mg (C_{max} of 0.181 μg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and 3 phase 2 studies have been completed. In addition, 6 clinical studies evaluating relugolix are ongoing, including 2 phase 1 studies, 2 phase 2 studies in men with prostate cancer (US and Europe), and 2 phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least one dose of relugolix, including 158 women receiving relugolix 40 mg once daily for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of testosterone in male subjects and estradiol in female subjects. After oral

administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The PK and pharmacodynamics of relugolix have been evaluated, and appear to be similar in Western and Asian volunteers, despite the lower mean body mass index observed in Asian volunteers.

A relative bioavailability and food effect study was conducted using the global phase 3 prostate cancer formulation of 120 mg relugolix. After administration with a high-fat, high-calorie breakfast, the C_{max} and AUC of relugolix were reduced, on average, by 21.4% and 18.8%, respectively.

In the phase 1 study C27001, serum LH, FSH, dihydrotestosterone, and testosterone concentrations were determined in healthy men following single and multiple oral doses of relugolix or placebo for up to 28 days. Loading doses of ≥ 160 mg on Day 1 were used to shorten the time to testosterone suppression. Relugolix caused an immediate and effective suppression of LH, FSH, and testosterone. After 14 days of once daily dosing, mean LH and serum testosterone concentration profiles were similar for the 40, 80, and 180 mg relugolix dose cohorts. LH, FSH, and testosterone concentrations began decreasing 2 to 6 hours postdose on Day 1 and remained suppressed through Day 14. However, the relugolix once daily maintenance dose was a major determinant of sustained testosterone suppression. Profound castration (defined as average testosterone levels < 20 ng/dL or 0.7 nmol/L) was achieved with 40, 80, or 180 mg once daily for 14 days; however, 20 mg once daily was insufficient in maintaining adequate suppression of serum LH and testosterone concentration levels during the second week.

In healthy, older men receiving 14 or 28 days of dosing, effective castration was consistently achieved over 14 and 28 days dosing at daily doses of 40 to 180 mg (14 days) and 80 to 160 mg (28 days). Use of a loading dose for up to 3 days (or once daily doses of ≥ 160 mg) resulted in castration levels of testosterone (< 50 ng/dL or 1.7 nmol/L) within 24 to 48 hours. Results obtained after 28 days of dosing suggested that the likely minimal, fully effective maintenance dose for sustained castration would be relugolix ≥ 80 mg once daily. Doses of 80 mg and 120 mg were moved forward into phase 2 development.

Relugolix is to be administered in the fasted state (at least 1 hour before or 2 hours after a meal), as food decreases the extent of relugolix absorption by approximately 20%. The exposure of relugolix is increased by inhibitors of P-glycoprotein up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 (CYP) 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong QTc at single doses of 60 or 360 mg.

2.2.4.2. Clinical Studies in Men with Prostate Cancer

One phase 1 study and 2 phase 2 studies have been conducted evaluating relugolix in men with prostate cancer.

Study TB-AK160108 is an ongoing multicenter phase 1, open-label, dose range-finding study conducted in hormone treatment-naïve Asian patients with non-metastatic prostate cancer. The study consists of a dose-rising phase (Part A) and an expansion phase (Part B). In Part A, a loading dose of relugolix (320 or 360 mg) was administered on Day 1 followed by once daily dosing on Days 2 through 28, with the dosage dependent on the individual cohort of 3 to 4

patients each. In Part B, 30 patients receive a maximum of 96 weeks treatment at doses of 80 and 120 mg once daily (N = 15 each arm, loading dose of 320 mg on Day 1). Testosterone reduction by both doses of relugolix was rapid and sustained through 48 weeks. Both the 80- and 120-mg once daily doses were evaluated in phase 2 clinical studies.

Study C27003 is a phase 2 study that enrolled men in North America or the United Kingdom requiring 6 months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily following a single oral loading dose of 320 mg (N = 65) or to degarelix 80 mg subcutaneously every 4 weeks following a single loading dose of 240 mg (N = 38) for 24 weeks. External beam radiation therapy was initiated for most patients between Week 13 and Week 15.

Relugolix 120 mg administered orally once daily rapidly suppressed testosterone levels below the castration threshold (50 ng/dL [1.7 nmol/L]) within the first week of therapy and maintained those levels from the end of Week 4 through at least 24 weeks. The levels of testosterone suppression achieved by relugolix were similar to those achieved by monthly injections of degarelix. Profound castration rates below the lower testosterone threshold of < 20 ng/dL (0.7 nmol/L) were also similar in the relugolix and degarelix groups (Table 2-1).

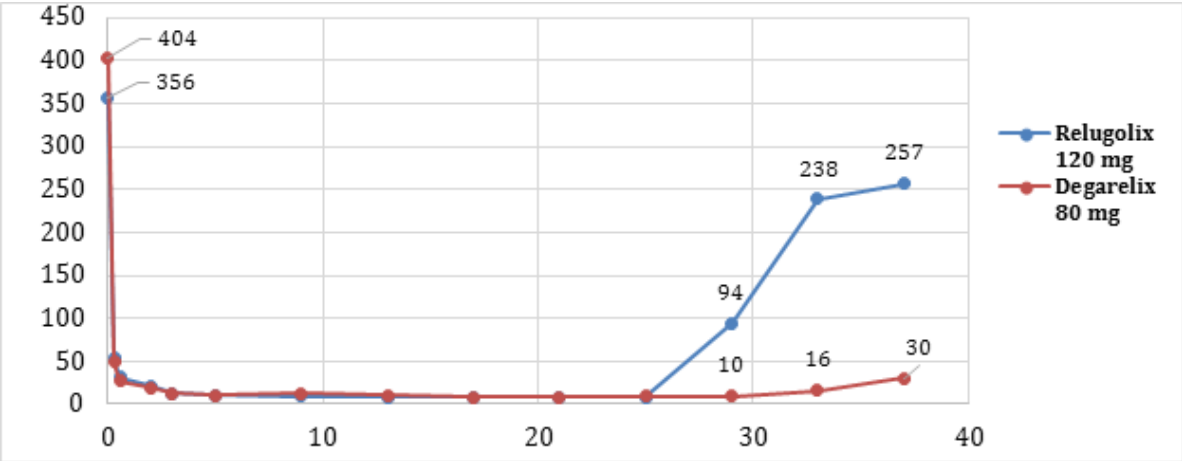
Table 2-1 Study C27003: Sustained Castration Rates (Percentage of Men Achieving Testosterone Suppression to < 50 ng/dL [1.7 nmol/L]) through 24 Weeks

	Relugolix 120 mg QD[a] N = 65	**Degarelix 80 mg Q4W[b] N = 38**
Castration rate over 24 weeks, % (95% CI)	95% (87.1, 99.0)	89% (75.2, 97.1)

Note: Castration rate is defined as the estimated proportion of patients who have testosterone concentrations < 50 ng/dL at all scheduled visits Week 5, Day 1 to specific time point (Week 25, Day 1).
Abbreviations: CI, confidence interval; Q4W, once every 4 weeks; QD, once daily
a. Loading dose of 320 mg on Day 1
b. Loading dose of 240 mg on Day 1, then dosed every month

The percentage PSA reductions and absolute PSA values over time were consistent with the rapid testosterone reductions observed with both therapies and were similar between the relugolix and degarelix treatment arms. Prostate gland size was measured during screening and following 8 to12 weeks of study drug treatment. In both treatment groups, the average reduction in estimated prostate volumes was similar, approximately 30%. Following discontinuation of therapy at the end of 24 weeks, patients were followed for an additional 12 weeks to evaluate testosterone recovery and associated changes in PSA and quality of life. At the end of the follow-up period, approximately half of the patients receiving relugolix had recovered either to the baseline testosterone value or to > 280 ng/dL, whichever was less, compared to only 6% of patients receiving degarelix (Figure 2-1).

Figure 2-1 Study C27003: Testosterone Recovery Following Discontinuation of Relugolix and Degarelix at Week 25



Note: Y-axis shows testosterone value (ng/dL); x-axis shows study week.

Study C27002 is a phase 2 study of relugolix and leuprolide acetate in patients with prostate cancer who require first-line androgen deprivation therapy, which is ongoing in North America. This study was designed to help plan the population, dosing, and assessment schedules for phase 3 studies in patients with advanced prostate cancer. Eligible patients in C27002 have evidence of advanced prostate cancer including either: 1) PSA biochemical relapse following primary surgical or radiation therapy of curative intent; 2) newly diagnosed metastatic prostate cancer; or 3) advanced localized disease for which immediate radiation or surgical therapy is not indicated. In this open-label, parallel group study, patients were randomized to receive 1 of 2 dose levels of oral relugolix (80 or 120 mg [patients randomized to relugolix received a loading dose of 320 mg on Day 1], N = 50 per group) or to an observation cohort to receive standard GnRH therapy with leuprolide acetate 22.5 mg administered by intramuscular injection every 12 weeks (N = 25). Relugolix or leuprolide acetate was administered for up to 48 weeks with patients randomized to leuprolide acetate receiving their last on-study 12-week depot injection at Week 37.

The primary objective of this phase 2 study was to evaluate the ability of relugolix to achieve and maintain testosterone suppression (< 50 ng/dL [1.7 nmol/L]) through Week 25. Results from the completed study C27002 demonstrate that both doses of relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold within the first week of therapy and maintained those levels in 91% of patients through 24 weeks of treatment (Table 2-2).

Table 2-2 Study C27002: Castration Rates (Percentage of Men Achieving Testosterone Suppression to < 50 ng/dL [1.7 nmol/L] through 24 Weeks)

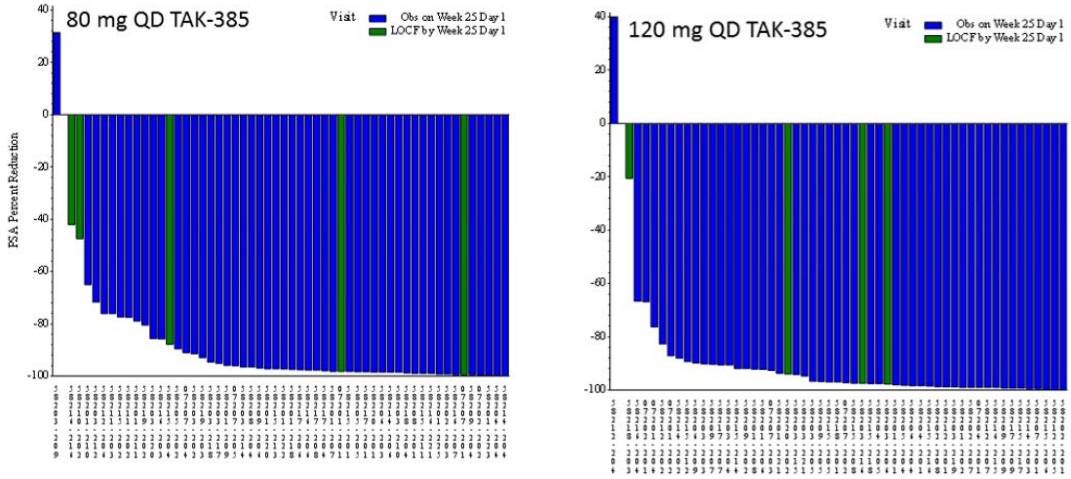
	Relugolix			Leuprolide Acetate 22.5 mg Q12W N = 24
	80 mg QD N = 56	120 mg QD N = 54	Total N = 110	
Patients with at least 1 dose of treatment, n	56	54	110	24
Castration rate[a] over 24 weeks				
n (%)	51 (91)	49 (91)	100 (91)	23 (96)
95% CI[b]	80.4-97.0	79.7-96.9	83.9-95.6	78.9-99.9
Profound castration rate[c] over 24 weeks				
n (%)	39 (70)	41 (76)	80 (73)	18 (75)
95% CI[b]	55.9-81.2	62.4-86.5	63.4-80.8	53.3-90.2

Abbreviations: CI, confidence interval; Q12W, once every 12 weeks; QD, daily

a. Castration rate was defined as the estimated proportion of patients who have testosterone concentrations < 50 ng/dL at all scheduled visits Week 5 Day 1 to specific time point.
b. The 2-sided 95% CI was calculated using the normal approximation method, if the number of non-castration patients was = 5 in any treatment arm, the exact CI was presented.
c. Profound castration rate was defined as the estimated proportion of patients who had testosterone concentrations < 20 ng/dL at all scheduled visits Week 13 Day 1 through specific time point.

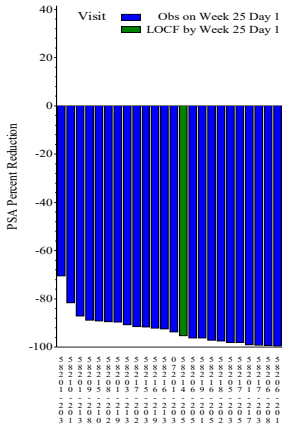
Castration to below the lower testosterone threshold of < 20 ng/dL was also similar in the 2 relugolix arms and to that observed in the leuprolide acetate arm. On average, in patients receiving relugolix, testosterone decreased to below the castration threshold of 50 ng/dL (1.7 nmol/L) by the Day 4 visit, and to below the profound castration threshold of 20 ng/dL (0.7 nmol/L) by the Week 5 visit. In contrast, in patients receiving leuprolide acetate, testosterone levels rose during the first 1 to 2 weeks of therapy and then declined to castrate levels by Week 5. PSA responses between the 2 relugolix arms and leuprolide acetate were similar as demonstrated by PSA waterfall plots showing the reduction in PSA from baseline for individual patients (Figure 2-2 [relugolix] and Figure 2-3 [leuprolide acetate]).

Figure 2-2 Study C27002: Waterfall Plots of Prostate-Specific Antigen Percent Reduction by Dose of Relugolix at Week 25 Day 1



Note: Last observation carried forward method was used to impute percent prostate-specific antigen reductions for patients without an observation at Week 25 Day 1.
Abbreviations: LOCF, last observation carried forward; Obs, observed; PSA, prostate-specific antigen; QD, once daily; TAK-385, relugolix

Figure 2-3 Study C27002: Waterfall Plot of Prostate-Specific Antigen Percent Reduction by Leuprolide Acetate at Week 25 Day 1



Notes:
The leuprolide acetate dose was 22.5 mg every 12 weeks.
Last observation carried forward method was used to impute percent prostate-specific antigen reductions for patients without an observation at Week 25 Day 1.
Abbreviations: LOCF, last observation carried forward; Obs, observed; PSA, prostate-specific antigen

A more detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix

Investigator Brochure, Version 9.0, dated 09 November 2016, along with a full discussion of the safety profile of relugolix.

2.2.4.3. Clinical Safety of Relugolix in Men with Prostate Cancer

A full description of the safety data for relugolix from clinical trials is available in the Investigator Brochure. Overall, approximately 632 healthy volunteers (330 women, 302 men), 535 female patients with uterine fibroids (N = 229) or endometriosis (N = 306), and 218 male patients with prostate cancer received at least 1 dose of relugolix. Data from the 175 patients with prostate cancer who received relugolix in randomized, open-label, parallel-group phase 2 studies, C27002 and C27003, provide the basis for the frequency of expected adverse events associated with relugolix in the prostate cancer indication. The adverse drug reactions in the prostate cancer indication observed in the phase 2 studies include hot flush (59%), fatigue (26%), arthralgia (10%), nausea (5%), and gynecomastia (3%). No clinical evidence of PLD has observed in any relugolix clinical study.

Leuprolide Acetate Depot 3-M

Leuprolide acetate depot is indicated for the palliative treatment of advanced prostatic cancer.

Leuprolide acetate acts as an agonist at pituitary GnRH (gonadotropin-releasing hormone) receptors. Leuprolide acetate has greater receptor affinity, reduced susceptibility to enzymatic degradation, and is approximately 100-fold more potent than the natural GnRH molecule. GnRH agonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, causing an initial release of both LH and FSH, which causes a subsequent increase in testosterone production from testicular Leydig cells. Initially, leuprolide acetate stimulates LH production, which in turn causes a surge of testosterone and dihydrotestosterone for 5 to 12 days before the ultimate inhibition of LH. This androgen surge of male hormones can cause a flare reaction ("clinical flare"), which may lead to an increase in bone pain, bladder obstruction, or other symptoms due to prostate cancer [Tolis, 1982; Schally, 1980; Waxman, 1985; Conn, 1991; Limonata, 2001].

Chronic stimulation by the GnRH agonist ultimately desensitizes the GnRH receptors, downregulating the secretion of gonadotropins, LH, and FSH, leading to hypogonadism and thus a dramatic reduction in testosterone and dihydrotestosterone, on which continued growth of prostate cancer cells depends. The fall in serum LH leads to a decrease in serum testosterone to castrate levels within 3 to 4 weeks after the start of treatment. Continued treatment maintains serum testosterone at castrate levels.

The decrease in testosterone production is generally reversible over time upon cessation of GnRH agonist therapy. However, testosterone production does not always return to baseline levels and may be related to the duration of GnRH agonist therapy, patient age, and other factors.

The flare phenomenon can be effectively prevented with antiandrogen therapy, which blocks the effect of the increased serum testosterone [Loblaw, 2004]. First generation antiandrogens such as flutamide, bicalutamide, and nilutamide bind to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone. They are often used in an attempt to limit the clinical sequelae produced by the hormonal surge resulting from GnRH agonist treatment.

The most common adverse reactions (> 10%) reported for marketed formulations of leuprolide acetate depot in common use include the following examples:

- Leuprolide (leuprorelin) acetate 11.25 mg: weight fluctuation, hot flash, hyperhidrosis, muscle weakness, bone pain, decreased libido, erectile dysfunction, testicular atrophy, fatigue, injection site reaction [Prostap 3 DCS, 2016]
- Leuprolide acetate 22.5 mg: general pain, injection site reaction, hot flashes/sweats, gastrointestinal disorders, joint disorders, testicular atrophy, urinary disorders [Lupron Depot, 2016]

In post marketing experience, mood swings, depression, rare reports of suicidal ideation and attempt, rare reports of pituitary apoplexy, and rare reports of serious drug induced liver injury have been reported. A risk of developing or worsening diabetes has been reported in men receiving this class of drug.

The package insert (approved labeling) for the leuprolide acetate study drug provided for this study should be referenced for warnings, precautions, and safety information.

3. STUDY OBJECTIVES AND ENDPOINTS

This phase 3 trial has 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit as listed briefly below and described in detail in the statistical analysis plan. Patients enrolled into this phase 3 trial will be randomized 2:1 to either relugolix 120 mg once daily following an oral loading dose of 320 mg on Day 1, or to leuprolide acetate 22.5 mg (or 11.25 mg in some Asian countries) 3-M depot injection. Patients randomized to leuprolide acetate will also receive an antiandrogen if indicated at the discretion of the investigator.

The first criterion for the primary efficacy endpoint will evaluate only patients randomized to relugolix. The second criterion for the primary efficacy endpoint will evaluate the non-inferiority of patients randomized to relugolix to those randomized to leuprolide acetate as described below.

Objectives	Endpoints
Primary	
• To evaluate the ability of relugolix to achieve and maintain serum testosterone suppressed to castrate levels of ≤ 50 ng/dL (1.7 nmol/L) in patients with androgen-sensitive advanced prostate cancer.	The primary endpoint is the sustained castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). • Evaluation Criterion 1: to determine whether the sustained castration rate (defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL [1.7 nmol/L] while on study treatment from Week 5 Day 1 through Week 49 Day 7) for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be at least 90% to meet this criterion. • Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot injection as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.
Secondary	
• To evaluate the time course and change in serum testosterone during treatment with relugolix;	• Describe effects on serum testosterone: o Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4, prior to dosing on Week 2, and prior to dosing on Week 3; o Profound castration rate defined as the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) while on treatment from Week 25 Day 1 through Week 49 Day 1);

Objectives	Endpoints
• To evaluate the time course and magnitude of PSA reduction during treatment with relugolix;	• Describe effects on PSA: o Proportion of patients with confirmed PSA response (by Prostate Cancer Clinical Trials Working Group 3 [Scher, 2016]) at the Week 2 and 5 visits; o Proportion of patients with PSA concentration < 0.2 ng/mL [0.2 µg/L] at the Week 25 visit;
• To evaluate testosterone recovery following discontinuation of relugolix;	• Time to testosterone recovery in the first 100 patients randomized to relugolix and the first 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of leuprolide acetate 3-M depot);
• To evaluate quality of life using validated patient-reported outcome instruments;	• Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable during the Follow-up and/or End of Treatment visits; • Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as the EuroQol EQ-5D-5L questionnaire, at regular intervals during treatment, and as applicable during the Follow-up visits;
• To evaluate the safety of relugolix 120 mg once daily in men with androgen-sensitive advanced prostate cancer;	• Incidence of adverse events; • Incidence of abnormalities in clinical laboratory data;

Objectives	Endpoints
• To evaluate the effect of relugolix and leuprolide acetate on endocrine pharmacodynamic parameters;	• Endocrine marker effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for: o LH at the Week 2, Week 3, and Week 5 visits, and then every 4 weeks until the last follow-up visit; o FSH at the Week 5, Week 13, Week 25, Week 37, and Week 49 visits; o Dihydrotestosterone at the Week 5, Week 13, Week 25, Week 37, and Week 49 visits; o Sex hormone binding globulin at the Week 13, Week 25, and Week 49 visits;
• To collect relugolix plasma concentration data to further evaluate relugolix population PK and the relationship between relugolix exposure and serum testosterone; and	• Predose relugolix plasma concentrations;
• To characterize the relugolix plasma PK parameters in a subset of patients from China and Japan.	• Single and repeat-dose plasma relugolix PK parameters such as C_{max}, $AUC_{0-\tau}$, and t_{max} in a subset of patients from China and Japan.
Exploratory	
• To explore the overall survival of patients treated with relugolix; and	• Overall survival defined as time from randomization to date of death prior to data cutoff date;
• To explore the contribution of genetic variance on drug response.	• The presence of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The HERO study is a phase 3 multinational randomized, open-label, parallel-group study to evaluate the safety and efficacy of relugolix in patients with androgen-sensitive advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy. Relugolix is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist that lowers testosterone by inhibiting pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Relugolix 120 mg orally once daily or leuprolide acetate depot suspension 22.5 mg (or 11.25 mg in some Asian countries) every 3-months (3-M) by subcutaneous or intramuscular injection will be administered to patients with prostate cancer who require

androgen deprivation therapy. This study will evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) for 48 weeks in patients with androgen-sensitive advanced prostate cancer.

To be eligible for the study, a patient must be, in the opinion of the investigator, a candidate for at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer and must not be a candidate for surgical therapy. Eligible patients include those with evidence of biochemical relapse (rising PSA) following local primary intervention with curative intent, newly diagnosed metastatic disease (excluding metastases to the brain), and/or advanced localized disease. Patients may receive radiotherapy, cryotherapy or high frequency ultrasound no sooner than 2 months after initiation of androgen deprivation therapy. Patients may be included if they have not previously received androgen deprivation therapy for more than 12 months, and if the androgen deprivation therapy was completed at least 12 months prior to baseline. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy. Baseline serum testosterone must be ≥ 150 ng/dL (5.2 nmol/L) to be enrolled.

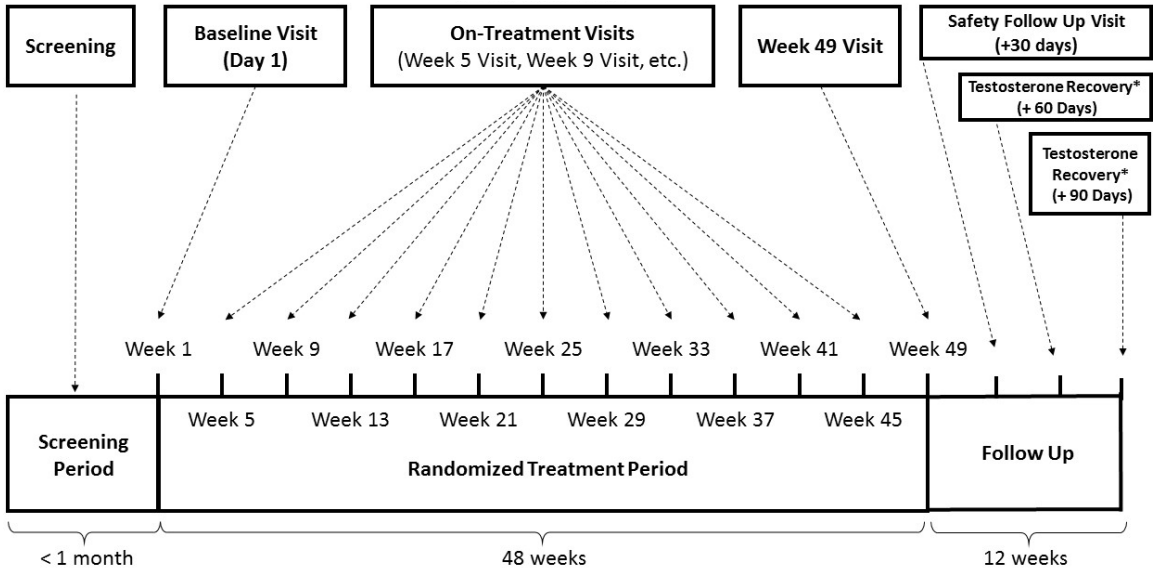
Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg once daily following a loading dose of 360 mg on Day 1 or leuprolide acetate 22.5 mg (or 11.25 mg in some Asian countries) 3-M depot subcutaneous or intramuscular injection, respectively, plus an antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator. Randomization will be stratified by geographic region, presence of metastatic disease, and age.

Approximately 1125 patients will be enrolled in this study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region. The study includes a Screening Period of up to 28 days, a Treatment Period of 48 weeks, and a Follow-up Period of up to 90 days. Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed. Eligible patients will receive study treatment for 48 weeks. During that time, testosterone and PSA will be assessed monthly and patient-reported outcomes (EORTC-QLQ-C30, EORTC-QLQ-PR25, EuroQol EQ-5D-5L) will be assessed approximately every 3 months during the Treatment Period and more frequently during the Follow-up Period. Additional serum endocrine evaluations will include: LH, FSH, dihydrotestosterone, and sex hormone binding globulin. Relugolix PK samples will be collected throughout the study. Full PK profiles will be determined in a subset of patients in China and Japan. Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead ECG, and visual acuity tests.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (testosterone level ≤ 50 ng/dL [1.7 nmol/L]), should remain on study and may receive additional oral therapy, systemic antineoplastic, and/or radiotherapy as prescribed by the investigator.

A schematic of the overall study design is provided in Figure 4-1.

Figure 4-1 Schematic of Study Design



Relugolix dosed daily (Baseline Day 1 – Week 48 Day 7)
Leuprolide Acetate dosed every 12 weeks (Baseline Day 1, Week 13 Day 1, Week 25 Day 1, and Week 37 Day 1)
*+60 Days and +90 Days Testosterone Recovery visits in subset of patients

4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is designed to establish the safety and efficacy of relugolix 120 mg orally once daily in men with advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy for androgen-sensitive disease. This study will focus on the primary objective of evaluating the ability of relugolix to achieve and maintain suppression of serum testosterone to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) in patients with advanced prostate cancer. During the Treatment Period of the study (Day 1 to Week 49 [Study Day 337]), patients will be randomized to one of the study treatment arms: oral loading dose of relugolix (360 mg) followed by 120 mg once daily of relugolix or leuprolide acetate 3-M depot injection of 22.5 mg (or 11.25 mg in some Asian countries) at 12-week intervals for 48 weeks. Patients treated with leuprolide acetate will also receive an antiandrogen for 4 weeks or longer if indicated in the opinion of the investigator.

The study is designed to allow for global approvals, however, different regulatory agencies require different criteria for the demonstration of efficacy. The United States (US) Food and Drug Administration (FDA) requires, for approval, a primary efficacy criterion to determine whether the sustained castration rate (defined as the cumulative probability of testosterone ≤ 50 ng/dL [1.7 nmol/L] while on relugolix study treatment from Week 5 Day 1 through Week 49 Day 1) is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion. The study includes a leuprolide acetate arm to meet the regulatory requirement of other regions to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot injection as

assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.

The dose of relugolix selected is based on data from phase 1 and 2 studies demonstrating that oral doses of 80 mg and 120 mg once daily following an oral loading dose of 320 mg were able to suppress testosterone to castrate levels (see Section 2.2.4.2 and the Investigator Brochure). A loading dose of 360 mg (three 120-mg tablets) was selected for phase 3 so that only one tablet size was required. Leuprolide acetate 3-M depot injection was selected as the comparator as this is the GnRH agonist used most commonly as standard of care in the population under evaluation. Degarelix, an injectable GnRH antagonist, was considered, but was not used as it has limited market uptake attributed at least in part to a significant number of injection site reactions.

4.3. Selection of Study Population

Approximately 1125 men with advanced prostate cancer requiring androgen deprivation therapy will be enrolled in this study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region. Enrollment is defined as the time at which a patient is randomized to a treatment group and receives at least one dose of study drug.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor prior to randomizing the patient.

4.3.1. Inclusion Criteria

A patient will be eligible for inclusion in this study only if all of the following inclusion criteria are met prior to randomization, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a male aged 18 years or older on the day of signing and dating the informed consent form;
3. Has histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate;

4. Is a candidate for, in the opinion of the investigator, at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer with one of the following clinical disease state presentations:
   a. Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, such as surgery, radiation therapy, cryotherapy, or high-frequency ultrasound and not a candidate for salvage treatment by surgery (radiotherapy, cryotherapy, or high frequency ultrasound are allowed after 2 months of androgen deprivation therapy); or
   b. Newly diagnosed androgen-sensitive metastatic disease; or
   c. Advanced localized disease not suitable for local primary surgical intervention with curative intent (radiotherapy, cryotherapy, or high frequency ultrasound are allowed after 2 months of androgen deprivation therapy);
5. Has a serum testosterone at the Screening visit of ≥ 150 ng/dL (5.2 nmol/L);
6. Has a serum PSA concentration at the Screening visit of > 2.0 ng/mL (2.0 µg/L), or, when applicable, post radical prostatectomy of > 0.2 ng/mL (0.2 µg/L) or post radiotherapy, cryotherapy, or high frequency ultrasound > 2.0 ng/mL (2.0 µg/L) above the post interventional nadir;
7. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at initial screening and at baseline (refer to Appendix 1);
8. Is a male patient who, even if surgically sterilized (ie, status post vasectomy):
   a. Agrees to use a male condom if having sex with a woman of childbearing age or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or
   b. Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception;
9. Must agree not to donate sperm from first dose of study drug through 4 months after the last dose of study drug;
10. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

4.3.2. Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

1. In the investigator's opinion, is likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating androgen deprivation therapy;
2. Previously received GnRH analog or other form of androgen deprivation therapy (estrogen or antiandrogen) for > 12 months total duration. If androgen deprivation therapy was received for ≤ 12 months total duration, then that therapy must have been completed at least 12 months prior to baseline;
3. Previous treatment for prostate cancer with a taxane-based regimen;
4. Metastases to brain per prior clinical evaluation;
5. Features of the patient's medical condition that make life expectancy due to other medical conditions of less than 5 years;
6. Scheduled for major surgery after baseline;
7. History of surgical castration;
8. Diagnosis of or treatment for another malignancy within the 2 years before baseline, or presence of another malignancy with evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection. Patients with Stage 0 or Stage 1 melanoma or superficial Stage 0 or Stage 1 bladder cancer, if curatively managed prior to screening, are not excluded. The medical monitor should be contacted for any questions regarding this exclusion criterion;
9. Abnormal laboratory values at the Screening visit that suggest a clinically unstable underlying disease, or the following laboratory values:
    a. Serum gamma-glutamyl transferase > 2.0 x ULN;
    b. Serum ALT and/or AST > 1.0 x ULN;
    c. Total bilirubin > 1.0 x ULN (unless secondary to Gilbert's syndrome or the pattern is consistent with a diagnosis of Gilbert's syndrome) or;
    d. Serum creatinine > 2.0 mg/dL;
10. Uncontrolled diabetes with HbA1c > 10% or previously undiagnosed diabetes mellitus with screening HbA1c > 8% (such excluded patients may be rescreened after referral and evidence of improved control of their condition);
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (hepatitis A virus IgM positive), hepatitis B (HBsAg positive), or hepatitis C (HCV antibody positive, confirmed by HCV ribonucleic acid);
12. Known human immunodeficiency virus infection;

13. Within 6 months before baseline, a history of myocardial infarction, angina, unstable symptomatic ischemic heart disease, or congestive heart failure, or any history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of Mobitz II second degree or third degree heart block without permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute); thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events); or any other significant cardiac condition (eg, pericardial effusion, restrictive cardiomyopathy). Patients with chronic stable atrial fibrillation on stable anticoagulant therapy or patients with stable cardiac rhythm controlled by a pacemaker are allowed;
14. The following ECG abnormalities are excluded:
    a. Q-wave infarction, unless identified 6 or more months before the Screening visit;
    b. QTc > 470 msec. If the QTc is prolonged in a patient with a pacemaker, the patient may be enrolled in the study upon discussion with the medical monitor; or
    c. Congenital long QT syndrome;
15. Uncontrolled hypertension despite appropriate medical therapy (sitting blood pressure of greater than 160 mmHg systolic and/or 100 mmHg diastolic at 2 separate measurements no more than 45 minutes apart during the Screening visit). Patients may be re-screened after referral and further management of hypertension;
16. Hypotension, as indicated by systolic blood pressure < 84 mmHg on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming upright position;
17. Bradycardia as indicated by a heart rate of < 45 beats per minute on the ECG at the Screening or Baseline Day 1 visit;
18. Treatment for prostate cancer with any investigational products within 12 months before the first dose of study drug (approved products under investigation for an alternative condition, not directly related to therapy for prostate cancer, may be allowed);
19. Treatment with an investigational product for indications other than prostate cancer within 3 months;
20. Previous treatment with relugolix in a clinical study;
21. Patient is a study site employee or is a primary family member (spouse, parent, child, or sibling) of a site employee involved in the conduct of the study;
22. Known gastrointestinal disease or procedure that could interfere with the oral absorption or tolerance of relugolix, including inability to swallow whole tablets;
23. Use of any medication listed in the prohibited medications table (see Section 5.10.1) without the appropriate washout period;
24. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;

25. Has a prior (within 1 year of the Screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
26. Any serious medical condition that limits life expectancy to less than 5 years, or any other medical or psychiatric condition that, in opinion of investigator, would interfere with completion of treatment according to this protocol.

4.4. Other Eligibility Criteria Considerations

Patient eligibility may require additional or repeat assessments such as safety labs, vital signs, or ECG during the Screening Period.

To assess any potential impact on patient eligibility with regard to safety, the investigator is referred to the Investigator Brochure for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) used in this study.

4.5. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the Screening Period. Study site personnel will access the interactive voice/web recognition system (IWRS) to assign a screening identification number to a potential patient.

For patients who provide informed consent and subsequently do not meet eligibility criteria, or withdraw consent are considered screen failures and are not randomized. Study site personnel should ensure that the source record includes documentation for the screen failure (eg, medical history, eligibility criteria, procedures performed).

Patient numbers assigned to patients who become screen failures are not to be reused. Patient identification numbers will be assigned to eligible patients at randomization, as described in Section 4.6.

4.6. Method of Assigning Patients to Treatment Group and Patient Identification Number

After a patient is screened and the investigator determines that the patient is eligible for enrollment, the site staff will complete the Randomization Authorization Form and send it to the sponsor (Myovant Sciences GmbH) or sponsor designee per the instructions in the Study Reference Manual. The sponsor (or designee) will approve the patient's enrollment in writing. Once the site has received approval, the patient may undergo the Baseline Day 1 visit. The site will randomize the patient to treatment by using the IWRS during the patient's Baseline Day 1 visit. The IWRS will assign the patient identification (ID) number. This number will identify the patient for the duration of the study. A study treatment kit number will be available at the site according to the randomization code.

4.7. Removal of Patients from Therapy

Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Week 49 visit on the Schedule of Activities. The End of Treatment is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.

Follow-up visits to assess safety will be performed in all study patients. If the patient plans to start alternative androgen deprivation therapy less than 30 days after the End of Treatment visit, the Safety Follow-up visit may occur earlier, before the start of the alternative androgen deprivation therapy. Testosterone recovery will be evaluated in the first 100 patients randomized to relugolix and 50 patients to leuprolide acetate who complete 48 weeks of study drug treatment and, in the opinion of the investigator, are candidates for intermittent androgen deprivation therapy and will not be offered alternative androgen deprivation therapy upon completion of study therapy. These patients will return for the 60- and 90-day follow-up Testosterone Recovery visits.

The safety and/or compliance events shown in Table 4-1 will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved.

Table 4-1 Removal of Patients from Treatment

Reason	Comment
Adverse event or intercurrent illness	Any intolerable adverse event to the patient that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued
Failed to meet eligibility criteria post randomization	If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health
Dose hold	Relugolix dose hold that exceeds 10 consecutive days
Patient not meeting criteria for testosterone suppression to castrate level	Patients with disease progression while on study drug, assuming adequate testosterone suppression (testosterone level ≤ 50 ng/dL [1.7 nmol/L]), may receive *additional* systemic antineoplastic therapy and may stay on study.

Reason	Comment
Laboratory abnormality defined by protocol: ALT or AST > 8 x ULN; or ALT or AST > 5 x ULN and persists for more than 2 weeks; or ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or INR > 1.5; or ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)	If any of these liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status).
Confirmed QTc prolongation of more than 500 msec, in the absence of a pacemaker, as read by a cardiologist	If QTc prolongation of > 500 msec in the absence of a pacemaker occurs, the ECG must be repeated. Confirmed QTc prolongation will result in removal of the patient from treatment.
Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist that may be related to study drug treatment	
Gross noncompliance with protocol	Patients who are, in the opinion of the investigator or the medical monitor, non-compliant with the protocol's requirements
Patient decision	Patients may permanently discontinue study treatment at any time for any reason. Following study drug discontinuation, patients should attend the protocol-required safety follow-up visit.
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime as described in Section 10.3.3. The sponsor will terminate this study following completion of study objectives, or earlier if deemed necessary.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; INR, international normalized ratio; QTc, QT interval corrected for heart rate; ULN, upper limit of normal

Once study drug has been discontinued, all study procedures outlined for the Week 49 visit will be completed as specified in the Schedule of Activities (Section 1.1). The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who withdraw from treatment will not be replaced.

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as

possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. Patients randomized to relugolix should be counseled to notify the investigator in the event of intercurrent illness to determine if the study drug treatment can be continued. Every effort should be made to ensure the patient's compliance with study drug treatment, including calling patients to reschedule missed visits.

In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should attempt at least 3 documented telephone calls and, if necessary, a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.8. Contraception/Pregnancy Avoidance

It is not known what effects relugolix has on human pregnancy or development of the embryo or fetus. Therefore, male patients should avoid impregnating a female partner.

A patient must use a condom if having sex with a pregnant woman. Patients must not donate sperm from first dose of study drug through 4 months after the last dose of study drug.

Nonsterilized male patients should use a male condom, either alone or in addition to effective methods of contraception used by a female partner of childbearing potential, through defined periods during and after study treatment as specified below. Examples of effective contraceptive methods include condoms, hormonal contraceptives, and intrauterine devices.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to one of the following:

- Use a male condom if having sex with a woman of childbearing age or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods for the female partner, and withdrawal are not acceptable methods of contraception.

5. TREATMENTS

5.1. Treatments Administered

Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg following a loading dose of 360 mg on Day 1, or leuprolide acetate 22.5 mg (or 11.25 mg in some Asian countries) 3-M depot injection (plus antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator). Randomization will be stratified by geographic region, presence of metastatic disease, and age**.**

Approximately 1125 patients will be enrolled in the study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region.

Study treatment is defined as either oral relugolix or leuprolide acetate injection (see Table 5-1).

Table 5-1 Description of MVT-601-3201 Study Drugs

	Study Treatment	
Product name:	Relugolix	Leuprolide Acetate 3-M Depot
Formulation description:	Round film coated pink tablet	
Dosage form:	Tablet	
Unit dose strength and dosage level:	120 mg, following a single-loading dose of 360 mg	22.5 mg (11.25 mg in some Asian countries)
Route of Administration / Duration	Oral / 48 weeks[a]	Subcutaneous or intramuscular / 48 weeks[a]

a. Duration of treatment is 48 weeks during the Treatment Period; the last leuprolide acetate injection occurs 12 weeks before the end of the Treatment Period.

5.2. Identity of Investigational Product

Relugolix has the chemical name N-(4-(1-(2,6-difluorobenzyl)-5-((dimethylamino)methyl)-3-(6-methoxy-3-pyridazinyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-6-yl)phenyl)-N'-methoxyurea.

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using the US Pharmacopeia and the National Formulary excipients.

5.3. Randomization and Stratification

Patients are assigned to one of 2 treatment arms in accordance with the randomization schedule using an integrated randomization system (IWRS).

At Baseline Day 1, patients will be randomized in a 2:1 ratio to one of the following treatment arms:

Treatment Arm	Randomized Treatment	Approximate Number of Patients
Arm A	Relugolix 360 mg (three 120 mg tablets) single oral loading dose on Day 1 followed by 120 mg orally once daily	744
Arm B	Leuprolide acetate, 22.5 mg 3-M depot[a] injection (or 11.25 mg in some Asian countries)	371

a. Antiandrogen is administered for the first 4 weeks or longer if indicated, in the opinion of the investigator.

Randomization will be stratified by geographic region, presence of metastatic disease, and age age as follows:

- Geographic Region
  - Europe;
  - North and South America; or
  - Asia and Rest of World.
- Presence of Metastatic Disease
  - Metastatic disease diagnosed on locally-read imaging by abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) or bone scan at the time of the Baseline Day 1 visit; or
  - No evidence of metastatic disease by locally-read imaging.
- Baseline Age
  - ≤ 75 years old; or
  - > 75 years old.

5.4. Directions for Administration

Relugolix

Relugolix 120-mg tablet strength will be available as immediate-release film-coated tablets. These tablets will be presented in 45-tablet bottle packaging and dispensed to patients every 4 weeks at scheduled study visits.

All protocol-specific criteria for administration of study drug must be met and documented prior to study drug administration. Study drug will be dispensed by study personnel only to eligible patients who are under the supervision of the investigator or identified subinvestigator(s). If a blood draw or any study procedure coincides with a meal, the study procedure will take precedence, followed by the blood draw, and then the meal.

At the Baseline Day 1 visit, the site will administer a single loading dose of oral relugolix 360 mg (3 tablets).

Patients randomized to relugolix will be instructed to take one tablet on an empty stomach at least 1 hour before breakfast once daily. If the dose is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

Patients may consume water ad libitum. Patients should swallow the study medication whole and not chew it or manipulate it in any way before swallowing.

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK and pharmacodynamic samples are collected.

Leuprolide Acetate

Leuprolide acetate 3-M depot injection, 22.5 mg (or 11.25 in some Asian countries), will be administered every 12 weeks. Leuprolide acetate 3-M depot will be administered on Day 1 at

the clinic, then at 12-week intervals (see Schedule of Activities, Section 1.1) and investigators should follow product instructions provided by the manufacturer. An antiandrogen may be administered for the first 4 weeks or longer if indicated, as determined by the investigator, and/or as indicated by disease status (eg, in patients with extensive localized symptomatic disease or with metastatic disease).

Possible antiandrogen options include, but are not limited to, bicalutamide, flutamide, and nilutamide.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that is related to study drug and cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted if the investigator believes it is in the best interest of the patient to interrupt relugolix dosing until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 10 consecutive days for evaluation and treatment of an adverse event. Patients may subsequently be re-started on study drug, with the written approval of the sponsor (or designee).

5.6. Dose Escalation, Dose Reduction, and Dose Interruption

Neither dose escalations nor dose reductions are allowed in the study.

Every effort should be made to continue relugolix administration through treatment-emergent adverse events unless they are grade 3 or 4 and related to study drug, or the investigator believes it is in the best interest of the patient to interrupt relugolix dosing. Of note, patients on leuprolide acetate 3-M depot injection continue to receive GnRH agonist therapy because it is impossible to discontinue treatment.

If the grade 3 or 4 adverse event improves to grade 0, 1, or 2 after holding the dose, or if the adverse event is no longer believed to be related to study drug, the patient may be rechallenged at the same dose at the discretion of the investigator and medical monitor. If the adverse event remains grade 3 or grade 4 after treatment discontinuation and the investigator continues to believe the adverse event is related to study drug, study drug treatment should be discontinued permanently.

5.7. Storage, Packaging, and Labeling

Relugolix will be packaged in bottles containing 45 120-mg tablets of relugolix. Additional details regarding the packaging of relugolix are provided in the Investigator Brochure and Study Reference Manual.

Leuprolide acetate 11.25 mg or 22.5 mg 3-M depot injection will be packaged and labeled for clinical trial use.

Relugolix medication should be stored in an appropriate, limited-access, secure location, protected from light, in the original bottles and within a temperature range at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15 to 30°C (59 to 86°F) as indicated on the label.

A daily temperature log of the drug storage area must be maintained every working day.

Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Patients will be instructed to store study drug at room temperature out of the reach of children.

Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Refer to the leuprolide acetate product labeling for information regarding the proper storage and handling of leuprolide acetate.

5.8. Blinding

Blinding is not applicable; this is a randomized open-label study.

5.9. Study Drug Accountability and Treatment Compliance

Patients should bring all unused study drug to each study visit. Study drug accountability will be conducted and results will be recorded as the primary source of study drug accountability. If a patient is persistently noncompliant with the study treatment, it may be appropriate to withdraw the patient from the study.

All patients should be reinstructed regarding dosing compliance during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-2 provides examples of medications that are prohibited prior to the first dose of study medication until the End of Treatment visit and the Follow-up Period is complete. This list is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class. Patients may "wash out" of these prohibited medications prior to dosing based on the periods provided in Table 5-2.

Any investigational agent for the treatment of prostate cancer, including agents that are commercially available for indications other than prostate cancer that are under investigation for the treatment of prostate cancer, are also prohibited for at least 12 months prior to the first dose of study medication.

Table 5-2 Prohibited Medications and Washout Periods

Drug Class	Examples		Minimum Washout Period
GnRH analogues	Leuprolide acetate injection[a] Goserelin acetate injection		12 months
GnRH antagonists	Degarelix		12 months
Antiandrogens[a]	Bicalutamide Flutamide	Nilutamide Enzalutamide[b]	12 months
CYP17 inhibitors	Abiraterone acetate + prednisone		12 months
Other androgen suppressing agents	Estrogens Ketoconazole	Megestrol acetate Progestogens	12 months
Class IA an III antiarrhythmics	Amiodarone Procainamide	Quinidine Sotalol	2 weeks (3 months for amiodarone)
Moderate and strong CYP3A and P-glycoprotein inducers	Bosentan Carbamazepine Efavirenz Etravirine Mitotane Modafinil Nafcillin	Phenobarbital Phenytoin Rifampin St John's Wort Primidone Rifabutin Rifapentine	2 weeks
Moderate/strong P-glycoprotein inhibitors	Amiodarone Azithromycin Captopril Carvedilol Clarithromycin Conivaptan Cyclosporin Diltiazem Dronedarone Eliglustat Erythromycin	Felodipine Itraconazole Ketoconazole Lapatinib Lopinavir/Ritonavir Quercetin Quinidine Ranolazine Ticagrelor Verapamil	2 weeks (3 months for amiodarone)
Herbal therapies	Chinese herbs Ginkgo biloba Ginseng	Kava kava Melatonin	2 weeks

Abbreviation: CYP, cytochrome P450

a. Unless randomized to leuprolide acetate control arm of this study. Antiandrogen therapy is permitted for the first 4 weeks or longer of leuprolide acetate treatment.

b. Enzalutamide is allowed for the treatment of castration-resistant disease that occurs on study (rising prostate-specific antigen in the setting of testosterone suppressed to castrate levels (≤ 50 ng/dL [1.7 nmol/L]).

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded. At a minimum, the drug generic name, dose amount, route of administration, start date, and stop date will be recorded in the source documents and the eCRF.

If alternative androgen deprivation therapy is initiated prior to 30 days after the last relugolix dose, record the alternative androgen deprivation therapy as a concomitant medication.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]), should be encouraged to remain on study and, if indicated, may receive systemic antineoplastic and or radiotherapy.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.6. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Section 1.1). The study is divided into 3 periods: Screening Period, Treatment Period, and Follow-up Period. Unscheduled visits may also occur as needed to evaluate patients.

6.2. Screening Period (Day -28 to Day -1)

The Screening Period will be from Day -28 through Day -1. At the Screening visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent before any study-specific procedures are conducted, unless the procedures are part of routine standard of care. The informed consent process must be documented in the patient's clinical record.

The investigator will assess and confirm the eligibility of each patient and determine that each patient will maintain study drug compliance during the treatment period. All screening procedures results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

The following assessments will be performed:

- Complete medical history, including detailed prostate cancer history;
- Vital signs, weight, and height;
- 12-lead ECG;
- ECOG performance assessment;
- Complete physical exam and visual acuity assessment;
- Abdominopelvic CT or MRI and bone scan if not previously done in the preceding 2 months prior to the Baseline Day 1 visit;

- Demographics;
- Laboratory data collection (see Section 1.1);
- Verify inclusion/exclusion criteria; and
- Concomitant medications and adverse events.

A Randomization Authorization Form must be submitted to the sponsor for approval prior to conducting the Baseline Day 1 visit.

6.3. Treatment Period (Day 1 to Week 49 [Study Day 337])

Baseline Day 1 Visit

Study site personnel should ensure that an approved Randomization Authorization Form is in the patient's file before proceeding with the randomization and Day 1 visit procedures. Patients will be randomized to either relugolix or leuprolide acetate 3-M depot injection 22.5 mg (or 11.25 mg in some Asian countries) (see Section 5.3).

The following assessments will be performed:

- Patient-reported outcome questionnaires (EQ-5D-5L, EORTC-QLQ-PR25, and EORTC-QLQ-C30)
  - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Medical history;
- Vital signs and weight;
- 12-lead ECG;
- ECOG performance assessment;
- Symptom-based physical examination;
- Laboratory collection (see Section 1.1);
- Verify inclusion/exclusion criteria;
- Concomitant medications and adverse events;
- Randomize the patient; and
- Study drug management:
  - If study drug administration is not logistically feasible on the same day as randomization, the patient must come to the clinic within 3 days of randomization for the required procedures and initiation of treatment. Day 1 will be defined as the day of randomization regardless of the first dose.
  - If the patient is randomized to relugolix, site personnel will administer a single loading dose of oral relugolix 360 mg (3 tablets) and then dispense study drug to the patient and instruct on daily dosing of 120 mg (1 tablet) and the importance of medication compliance (see Section 5.4);
  - If the patient is randomized to leuprolide acetate, site personnel will administer the injection in the clinic.

Day 4 and Weeks 2, 3, and 4 Visits (Visit Window ± 1 day)

The following assessments will be performed:

- Vitals signs;

- Symptom-based physical examination;
- Laboratory collection (see Section 1.1); and
- Concomitant medications and adverse events.

Weeks 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, and 45 Visits (Visit Window ± 7 Days)

Importantly, patients randomized to relugolix should be called 7 days before each visit to ensure the patient is compliant with study drug medication.

The following assessments will be performed:

- Patient-reported questionnaires will be completed on the electronic tablet provided (Weeks 5, 13, 25, and 37 only)
  - Patients will complete the questionnaires before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs, weight
  - Weight will be collected only on Weeks 13 and 25;
- 12-lead ECG (Weeks 5, 13, and 25 only);
- ECOG performance assessment (Week 25 only);
- Symptom-based physical examination (except Week 25);
- Complete physical exam and visual acuity assessment (Week 25 only);
- Laboratory collection (see Section 1.1)
  - Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose; patients will be required to arrive at the clinic on an empty stomach;
- Concomitant medications and adverse events; and
- Study drug management:
  - For patients randomized to relugolix,
    - Perform study drug accountability;
    - Dispense study drug to patient, ensure the patient takes their daily 120 mg dose at the clinic under fasting conditions, at least 1 hour before or 2 hours after eating a meal and remind patient on importance of medication compliance.
  - For patients randomized to leuprolide acetate,
    - Site will administer leuprolide acetate in clinic every 12 weeks (Weeks 13, 25, and 37).

Week 49 or (Early Termination of Study Drug) (Visit Window ± 7 Days)

- For patients receiving relugolix, a member of the site team will call the patient 7 days before the Week 49 visit to remind the patient of the need for compliance with their study medication;
- Patient-reported outcome questionnaires
  - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs, weight;
- 12-lead ECG;
- ECOG performance assessment;
- Complete physical exam and visual acuity assessment;

- Laboratory collection (see Section 1.1);
    - Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose; patients will be required to arrive at the clinic on an empty stomach;
- Concomitant medications and adverse events; and
- Study drug management:
    - For patients randomized to relugolix,
        - Perform study drug accountability.

6.4. Follow-up Period

The study day in which the Follow-up visit occurs is relative to when the patient takes his last dose of study drug. The End of Treatment is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.

30-Day Safety Follow-up Visit (Visit Window ± 7 Days)

A Safety Follow-up visit should occur 30 days after the End of Treatment and may occur earlier for patients who are starting alternative androgen deprivation therapy or do not complete 12 weeks of study treatment. Adverse events should continue to be collected and recorded through 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Serious adverse events and concomitant medications will be collected from the signing of the informed consent form until the Safety Follow-up visit approximately 30 days after the last dose of study drug.

All other study procedures should be completed before the start of alternative androgen deprivation therapy.

The following assessments will be performed:

- Patient-reported questionnaires
    - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs and weight;
- 12-lead ECG;
- ECOG performance assessment;
- Symptom-based physical examination;
- Laboratory collection (see Section 1.1); and
- Concomitant medications and adverse events.

Testosterone Recovery Visit (Visit Window ± 7 Days)

Patients who have started alternative androgen deprivation therapy will not participate in the 60- and 90-day follow-up visits. The first 100 patients randomized to receive relugolix and 50 patients randomized to receive leuprolide acetate who complete the 48 weeks of study drug treatment and, in the opinion of the investigator, are candidates for intermittent androgen deprivation therapy will be included in the Testosterone Recovery 60- and 90-day Follow-up visits. These patients will discontinue relugolix after 48 weeks of treatment and will be offered a period off androgen deprivation therapy.

The following assessments will be performed:

- Patient-reported outcome questionnaires
  - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs;
- Symptom-based physical examination;
- Laboratory collection (see Section 1.1); and
- Concomitant medications.

Health Status Survey

During the final weeks prior to database lock, sites will be asked to contact all study participants or their immediate family regarding the current health status of previously enrolled/completed study patients. If the site is unsuccessful in contacting the patient and/or immediate family, the site may access hospital records or publicly available sources such as national registries, newspaper obituaries, and social networking websites.

6.5. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the patient's source documentation. The following activities should be completed at an Unscheduled visit conducted to evaluate adverse events: vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment and collection of a PK sample if indicated, 12-lead ECG, recording of concomitant medications, and study drug compliance.

6.6. Study Procedures

6.6.1. Efficacy-Related Procedures

6.6.1.1. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, testosterone, dihydrotestosterone, sex hormone binding globulin, and PSA will be collected predose at the visits indicated in the Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. Testosterone samples may be analyzed at a second laboratory to confirm non-castrate levels (Section 1.1).

Serum LH, FSH, dihydrotestosterone, sex hormone binding globulin, and PSA samples will be analyzed at a central laboratory.

PSA will also be used to evaluate biochemical progression per Prostate Cancer Clinical Trials Working Group 3 guidelines [Scher, 2016].

Analysis of serum samples for testosterone is detailed below:

Testosterone Assessment

Serum concentrations of testosterone will be obtained as indicated in the Schedule of Activities (see Section 1.1).

Testosterone will be assayed using a liquid chromatography-tandem mass spectrometry method sensitive at least as low as 5 ng/dL (0.17 nmol/L) for all measurements.

Between Week 5 and Week 49 visits (inclusive), testosterone samples that are above castrate level (> 50 ng/dL) will be reported to the investigator at the respective study site. Testosterone samples may be subject to reanalysis by liquid chromatography/mass spectrometry and/or immunoassay sensitive to at least as low as 10 ng/dL.

Instructions for collection and processing of blood specimens are provided in the Study Reference Manual.

6.6.1.2. Relugolix Pharmacokinetic Sample Collection

Pharmacokinetic samples will only be collected in patients randomized to relugolix study drug.

Blood samples for pharmacokinetic analysis of relugolix will be collected at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients will be instructed to take their dose of study drug in the clinic at these visits. Study drug will be administered on an empty stomach or at least 2 hours before food, and food will be withheld for 1 hour after dosing. The date and time of their previous dose of study drug (ie, the dose the day before the clinic visit) will be accurately recorded. If the study patient inadvertently took the study drug at home on the morning of the clinic visit, the date and time of that dose should also be accurately recorded and the pharmacokinetic sample collected, which may be used for population PK modeling.

Plasma from the Week 5 and Week 13 visits in all patients will be analyzed for relugolix plasma concentration. Analysis of other individual patient plasma samples will be performed on a case-by-case basis (such as those patients with non-castrate testosterone levels).

Collection, processing, storage, and shipping instructions will be provided in the Study Reference Manual. Plasma analysis of relugolix will be performed by the sponsor (or designee).

China and Japan Pharmacokinetic Subset

In a subset of approximately 20 patients from China and approximately 20 patients from Japan that are randomized to relugolix, additional relugolix PK samples will be collected on Day 1, Day 4, and Week 2 visits (see Schedule of Activities in the protocol synopsis, Section 1.1). The actual date and time of study drug administration and the date and time of each PK sample will be accurately recorded.

All samples from the China and Japan subset will be analyzed for plasma relugolix concentrations. Collection, processing, storage, and shipping instructions will be provided in the Study Reference Manual. Plasma analysis of relugolix will be performed by the sponsor (or designee).

6.6.1.3. Pharmacogenomics Sample Collection

Whole Blood Sample for Germline Deoxyribonucleic Acid

Pharmacogenomic analysis may be conducted to examine the contribution of genetic variance on drug response, for example, its efficacy and safety. Participation of study patients in pharmacogenomic sample collection is optional. A pharmacogenomics sample will be collected from patients at all participating study centers, with individual patient consent and per local ethics and regulatory standards. The sample will be retained for germline deoxyribonucleic acid (DNA) analysis of potential genetic determinants of drug safety, drug efficacy or disease response, and drug metabolism.

Every patient must sign informed consent/be consented in order to participate in the sampling of whole blood for DNA analysis. This research may be used to develop a better understanding of the safety and efficacy of relugolix and other study drugs, to increase understanding of the disease/condition being studied, and for improving the efficiency, design and study methods of future research studies.

Two venous whole blood sample (3 mL per sample) for the analysis of germline DNA will be collected at Day 1 from all patients who have provided informed consent. The DNA samples are expected to be collected at the Day 1 visit, but if necessary, may be collected at any visit after randomization. If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible. Germline DNA analysis may be conducted to investigate the contribution of genetic variance on drug response, for example, its efficacy and safety. As pharmacogenomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples.

Individual blood samples for germline DNA analysis, including the result of any analyses and corresponding information will be identified only by a code in a computer database.

The whole blood samples for DNA analysis will be stored securely at the sponsor's location or its designated central laboratory vendor until 15 years after completion of this study (HERO, MVT-601-3201) and/or until the drug development of relugolix is no longer actively pursued by Myovant or its collaborators. The storage period for these samples may be adjusted by country in accordance with local regulatory and/or legal requirements for the storage of research samples. Such changes will be reflected in the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) country-specific informed consent form. After that time, the samples will be properly destroyed by the central laboratory or designee following approval by the sponsor. The investigator will keep records linking the patient identity with the samples for the time required by applicable law. Patients who consent and provide a pharmacogenomic sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time.

Directions for sample collection and handling can be found in the Study Reference Manual.

6.6.1.4. Quality of Life

European Quality of Life 5-Dimension 5-Level Assessment

The EuroQol EQ-5D-5L comprises 5 scales and an overall assessment of health status on a visual analogue scale (Appendix 2). The 5 scales include: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The original version, the EQ-5D-3L, includes 3 response options for each scale. However, a new 5-level response-option version, the EQ-5D-5L, has been developed with the following response options: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. It is believed that the EQ-5D-5L is superior to the EQ-5D-3L in terms of feasibility, ceiling effects, discriminatory power, and convergent validity. The EQ-5D-5L index values will be calculated from the EQ-5D-5L descriptive system scores based on the Crosswalk value sets [EuroQol Group, 1990; Brooks, 1996; Herdman, 2011; Janssen, 2013].

European Organisation for Research and Treatment of Cancer Assessments

The EORTC-QLQ-C30 [Fayers, 2001; Fayers, 2002] (Appendix 3) and the 25-item prostate cancer module EORTC-QLQ-PR25 [Spry, 2006] (Appendix 4) will be administered as specified in the Schedule of Activities (see Section 1.1).

The EORTC QLQ-C30 core measurement will be used to capture distal outcomes, including physical, social functioning, and overall health-related quality of life. The QLQ-C30 core questionnaire incorporates 30 questions comprising 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality of life scale. Several single-item symptom measures are also included. It is a reliable and valid measure of health-related quality of life in patients with cancer and takes about 11 minutes to administer. The instrument has been validated and used in many countries [Aaronson, 1993].

The EORTC-QLQ-PR25 is the 25-item Prostate Cancer module (P25) of the EORTC. The EORTC-QLQ-PR25 contains 3 additional symptom scales (urinary, bowel, sexual) and 5 treatment-related items.

6.6.2. Safety-Related Procedures

6.6.2.1. Weight, Height, and Body Mass Index

Height and weight will be measured during screening (within 28 days before the first dose of study drug). Weight will be obtained at additional time points as specified in the Schedule of Activities (see Section 1.1). Patients should have weight and height measured while wearing indoor clothing and with shoes removed.

6.6.2.2. Vital Signs

Vital sign measurements include oral temperature, pulse rate, and seated measurement of diastolic and systolic blood pressure. Patients should be sitting at rest for 5 minutes before blood pressure is measured. When vital sign measurements are scheduled at the same time as an ECG

and blood draw, the vital signs will be obtained immediately prior to the ECG and blood draw, and the blood draw will be collected at the scheduled time.

6.6.2.3. Physical Exams

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart, and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the baseline assessment. Visual acuity will be evaluated at Baseline Day 1, Week 25, and Week 49 by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment.

6.6.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the patient ID number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

Hematology	Serum Chemistry	Metabolic Panel
Hematocrit	Albumin	Total cholesterol
Hemoglobin	Alkaline phosphatase	High density lipoprotein cholesterol
Leukocytes with differential	ALT	Low density lipoprotein cholesterol
Neutrophils and absolute neutrophil count	AST	Triglycerides
Platelet (count)	Bilirubin (total)	Hemoglobin A1c
	Blood urea nitrogen	
	Calcium	
	Carbon dioxide	
	Creatinine	
	Chloride	
	Serum gamma-glutamyl transferase	
	Glucose	
	Lactate dehydrogenase	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	Urate	

Endocrine Panel	Diagnostic Screening (investigator's discretion)	
Serum testosterone Serum LH Serum FSH Serum sex hormone binding globulin	HIV test Hepatitis panel, including HBsAg and anti-HCV	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FSH, follicle-stimulating hormone; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LH, luteinizing hormone

A separate sample will be collected at the Day 1 visit and will be banked and tested for presence of hepatitis A, B, and C (hepatitis A antibody, IgM, hepatitis B core antibody, IgM, hepatitis B surface antigen, and hepatitis C antibody) if requested by the medical monitor for evaluation of abnormal liver function tests.

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, and plasma and serum hormone levels.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

6.6.2.5. 12-Lead Electrocardiograms

A 12-lead ECG will be administered at the time points specified in the Schedule of Activities (Section 1.1). When an ECG is scheduled at the same time as vital signs and a blood draw, the ECG will be obtained after the vital signs and prior to the blood draw; the blood draw will be collected at the scheduled time. ECGs will be read locally by a qualified physician.

If patients have a prolonged QTc (> 500 msec), the ECG should be repeated and confirmed. Patients with a confirmed QTc > 500 msec that develops during the trial should be withdrawn. All abnormal ECG findings must be documented by the investigator as clinically significant or not.

6.6.2.6. Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the eCRF from the beginning of screening until 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection. See Section 5.10.1 for a list of medications and therapies that are prohibited and/or allowed during the study.

6.6.2.7. Radiologic Assessment

CT imaging or MRI of the abdominopelvic region with contrast and a bone scan must be obtained prior to randomization for each patient to determine the presence or absence of metastatic disease. The scans should be read locally and do not need to be repeated if a scan exists within 60 days prior to the Baseline Day 1 visit.

Radiologic assessment is not included as part of the Schedule of Activities after randomization.

6.7. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of 5 mL of whole blood collected for pharmacogenomics testing (see Section 6.6.1.3) will be stored frozen at an appropriate vendor facility identified by the sponsor.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of his sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations including visual acuity assessment, vital signs, weight, ECGs, and clinical laboratory tests.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately); and

- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
  - Induces clinical signs or symptoms;
  - Requires active intervention; or
  - Requires interruption or discontinuation of study drug.

Events that **do not** meet the definition of an adverse event include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- The disease/disorder being studied, or expected progression;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen; and
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent).

Adverse events that occur during the study should be evaluated by the investigator and graded according to CTCAE (Appendix 5). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous". Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of study drug are permitted; however, study drug can be held for a period of up to 10 days for evaluation and treatment of an adverse event. The study drug may be restarted if deemed safe for the patient by the investigator.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events that jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local IRB/IEC.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's answers to the EQ-5D-5L will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record

each sign and symptom as an individual adverse event.

Overdose and pregnancy in a partner will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered until the Follow-up visit approximately 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first.

Serious adverse events will be collected from the signing of the informed consent form until the safety Follow-up visit approximately 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

Any event occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who continues to meet eligibility criteria and proceeds to dosing with study drug.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The definitions in Table 7-1 are to be used for the relationship of the adverse event to study drug.

Table 7-1 Causal Relationship to Study Drug

Relationship	Criteria
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (re-challenge) or withdrawal (de-challenge).
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE (see Appendix 5). For terms not specified with the CTCAE, the criteria in Table 7-2 should be used to determine the grade severity.

Table 7-2 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized Treatment Period or the Follow-up visit should be reported to the sponsor using the serious adverse event form within 24 hours of the study site personnel's knowledge of the event (see Section 7.6), even if the event does not meet serious adverse event criteria. Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 6.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or international normalized ratio (INR) >1.5
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1) AST or ALT increases to ≥ 3 x ULN; AND
2) Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3) Alkaline phosphatase value does not reach 2 x ULN; AND
4) No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease;
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus);
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
   - Alcoholic hepatitis;
   - Nonalcoholic steatohepatitis; or
   - Autoimmune hepatitis.

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

Using a serious adverse event report form, all serious adverse events must be reported within 24 hours of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study drug. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

The contact information for submission of serious adverse events and events of overdose or pregnancy of partner is available on the serious adverse event report form and is as follows:

Send completed Safety Report Forms to PRA Safety & Risk Management:

Site Location	Fax Number (Primary reporting method)	E-mail (Secondary reporting method)
North/South America: Europe, Asia, Pacific, and Africa:	PPD	PPD

For questions on serious adverse event/adverse event of clinical interest reporting, please call:

- North/South America: PPD or PPD
- Europe, Asia, Pacific, and Africa: PPD

The initial report should include:

- Study number (MVT-601-3201);
- Site name and number;
- Investigator name;
- Patient ID number, sex, and age;
- Details of study drug administration;
- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity); and
- Causal relationship to the study drug.

If the patient died, the report should include the cause of death and whether or not the cause of death was related to study drug, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 240 mg within a 24-hour window is an overdose, except for the 360-mg loading dose on Day 1. The sponsor does not recommend specific treatment for an overdose; supportive treatment should be provided as clinically applicable.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis); and
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If the partner of any patient becomes pregnant during the study or through 4 months after the last dose of study drug, the investigator must inform the sponsor of the pregnancy.

The patient should remain on study drug treatment, unless otherwise indicated.

If the patient agrees, the patient's pregnant partner should be notified and requested to sign a Release of Information form, permitting transfer of information regarding the pregnancy and outcome to the sponsor.

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the pregnancy reporting forms. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Benefit/Risk Assessment

Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

The risk assessment and mitigation strategies for this protocol are outlined in Table 7-3.

Table 7-3 Relugolix Potential Risks and Mitigation

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Stopping Criteria**
Hepatic Enzyme Increases Isolated increases in hepatic enzymes have been observed in prior clinical studies. Hepatic enzyme increases, considered an important potential risk of treatment with relugolix, are closely monitored in accordance with FDA guidelines for assessing drug-induced liver injury [FDA, 2009] in all relugolix studies.	Exclusion criteria for AST and ALT > 1 x the ULN; total bilirubin values > 1.0 ULN unless consistent with Gilbert's syndrome.	Liver chemistry will be monitored during the study. Appropriate liver stopping criteria and follow-up procedures are detailed in Section 7.5.2.
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual acuity will be evaluated during the study.
Risks Associated with Medical Castration Acute and subsequent chronic symptoms of medical castration (reduction of testosterone to ≤ 50 ng/dL [1.7 nmol/L]) include vasomotor symptoms or hot flushes, disturbed sleep related to vasomotor symptoms, decreased libido, and fatigue or loss of energy. These side effects are usually not severe and can be managed with anticipatory guidance. Long-term suppression of testosterone is associated with well-characterized risks including bone loss, decreased muscle mass, possible changes in insulin sensitivity with increased risk of diabetes, altered lipid metabolism, and possible increased risk of cardiovascular disease [Oefelein, 2002; Lopez, 2005; Diamond,1998; Keating, 2006; Braga-Basaria, 2006; Saigal, 2007; Tsai, 2007; D'Amico, 2007; Efstathiou, 2009].	-	Effects can usually be managed with appropriate anticipatory guidance (eg, diet and exercise programs) or supportive therapy when required (eg, lipid-lowering or bone-sparing agents).
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	-	Fasting lipids and glucose will be monitored during the study.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Stopping Criteria**
Loss of Bone Mineral Density Loss of bone mineral density is considered a potential risk of treatment with relugolix in the prostate cancer indication.	-	Fractures will be assessed through adverse event monitoring. Use of anti-resorptive bone therapy, such as bisphosphonates or denosumab, may be considered by the treating physician.

Abbreviations: ALT; alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; FDA, Food and Drug Administration; PLD, phospholipidoses; ULN, upper limit of normal

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the Study Reference Manual with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and Good Clinical Practices. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

8.3. Independent Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will review available safety data, as appropriate, on a periodic basis throughout the conduct of the study. Details of the Data and Safety Monitoring Board will be captured in a charter prior to the start of the study.

8.4. Steering Committee

A Steering Committee consisting of experts in the field of prostate cancer and staff members of Myovant Sciences GmbH will be established to provide oversight for the clinical trial, study design, study conduct, data analysis, and presentation and publication of the study data. Details of the Steering Committee responsibilities will be captured in a separate charter.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan will describe the detailed statistical methods and analyses for this study. The statistical analysis plan will be prepared and finalized prior to database lock and analysis of the primary and secondary endpoints.

All confidence intervals will be 2-sided at an alpha level of 0.05 unless otherwise specified. The methodology to be used to maintain a study-wide type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 2:1, relugolix to leuprolide acetate 3-M depot. Randomization will be stratified by the following factors:

- Geographic Region: North and South America versus Europe versus Asia and Rest of World;
- Presence of Metastatic Disease: yes versus no;
- Baseline Age: ≤ 75 years old versus > 75 years old.

Stratified efficacy analyses will incorporate these 3 stratification factors unless otherwise specified.

9.2. Analysis Populations

The Intent-To-Treat (ITT) population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. This will be the primary population used for the efficacy analysis. Patients will be analyzed according to their randomized treatment assignment.

The Per-Protocol population will consist of those members of the ITT population who have no major protocol deviations as defined in the statistical analysis plan, considering the following protocol deviations but not limited to:

- Those who entered the study even though they did not satisfy the entry criteria;
- Those who developed withdrawal criteria during the study but were not withdrawn;
- Those who received the wrong treatment or incorrect dose;
- Those who received an excluded concomitant treatment.

The Per-Protocol population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT population. The Per-Protocol population will be used as a sensitivity analysis of the ITT population for the primary efficacy endpoint and secondary endpoints. The Per-Protocol population will be identified prior to the database lock.

The primary population for safety analyses will be the Safety population, defined as all patients who receive at least one dose of any study treatment. Patients will be analyzed according to the treatment actually received, regardless of their randomized treatment assignment.

9.3. Efficacy Analyses

9.3.1. Primary Endpoint Analyses

The primary efficacy endpoint is the sustained castration rate, defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 (Study Day 337). This probability will be estimated for each treatment group using the Kaplan-Meier method with the confidence interval calculated using the exponential Greenwood formula via log-log transformation of the survival function. Patients who discontinue treatment prior to observing a testosterone level > 50 ng/dL (1.7 nmol/L) will be censored at the last testosterone assessment prior to discontinuation. Detailed censoring rules will be described in the statistical analysis plan.

There are 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit:

- Evaluation Criterion 1: to determine whether the sustained castration rate for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion.

- Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion. The confidence interval of the treatment difference will be calculated using the formula $\hat{V}\left[\widehat{S_1}(t) - \widehat{S_2}(t)\right] = \hat{V}\left[\widehat{S_1}(t)\right] + \hat{V}\left[\widehat{S_2}(t)\right]$, where each of the variance of the Kaplan-Meier estimate will be calculated using the Greenwood's formula $\hat{V}\left[\hat{S}(t)\right] = \hat{S}(t)^2\left[\sum_{j:t_{(j)}\leq t}\frac{d_j}{n_j(n_j-d_j)}\right]$; n_j denote the number of patients at risk at time $t_{(j)}$ and d_j denote the number of events observed at time $t_{(j)}$) [Lachin, 2000].

The evaluation criteria used for the primary efficacy endpoint assessment will be determined by regional regulatory requirements and will be prespecified in separate regional statistical analysis plans. The 2-sided type I error rates for the final analyses will be controlled at 0.05 separately for each regional analysis.

9.3.2. Secondary Endpoint Analyses

If the result of the primary endpoint is statistically significant, the secondary endpoints will be analyzed. The methods and procedures necessary to maintain a study-wide 2-sided type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

- Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing at Week 1 Day 4, prior to dosing at Week 2 Day 1, and prior to dosing at Week 3 Day1 will be summarized by treatment group using the Kaplan-Meier method;
- Profound castration rate defined as the cumulative probability of testosterone suppression of ≤ 20 ng/dL (0.7 nmol/L) while on treatment from Week 25 Day 1 through Week 49 Day 1 will be estimated for each treatment group using the Kaplan-Meier method. The difference in the cumulative probabilities between the relugolix group and the leuprolide acetate group will be provided, along with the 95% confidence interval calculated in the same manner as in the primary analysis of the primary endpoint;
- PSA response and percent change from baseline in PSA at Week 2 and Week 5 will be summarized and compared between the relugolix group and the leuprolide acetate group;
- Proportions of patients who have a PSA concentration < 0.2 ng/mL (0.2 µg/L) at Week 25 will be summarized by treatment group. The proportions will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in proportions;
- Time to testosterone recovery in the first 100 patients randomized to relugolix and the first 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not start alternative androgen deprivation therapy within the following

12 weeks (or within 24 weeks following the last received leuprolide acetate 3-M depot injection) will be compared between the relugolix group and the leuprolide acetate group;

- Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains will be summarized by treatment group. The least square means at Week 49 will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in the least square means using a mixed model for repeated measures; and
- Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as EQ-5D-5L will be summarized by treatment group. The least square means at Week 49 will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in the least square means using a mixed model for repeated measures.

Further details of the secondary analyses will be described in the statistical analysis plan.

9.4. Safety Analyses

The safety analyses will be based on the Safety population. Safety will be assessed by summarizing and analyzing adverse events, laboratory analytes, vital signs, ECG parameters, and concomitant medications.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ class using MedDRA 19.1 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used for analyses. The National Cancer Institute CTCAE will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the baseline versus post-baseline results.

9.5. Pharmacokinetic Analyses

Plasma relugolix concentrations will be listed and summarized and included in the clinical study report.

PK data will be pooled with data from other studies in healthy male patients and patients with prostate cancer for further population PK analysis, including evaluation of covariates of relugolix PK parameters, and for input into a population PK/pharmacodynamics models describing the

relationship between relugolix exposure and serum testosterone [Ahsman, 2016]. These population PK analyses will be detailed further in a separate statistical analysis plan and report.

For patients from China and Japan in the PK subset, plasma relugolix PK parameters C_{max}, $AUC_{0-\tau}$, and t_{max} from Day 1 and Day 14 of dosing will be determined. Population PK or PK/pharmacodynamic analyses may be conducted to explore the factors that affect relugolix exposure or to contribute to the assessment of the relationships between exposure and testosterone.

9.6. Endocrine Marker Analyses

Endocrine markers will be analyzed to see effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for:

- LH at Week 2, Week 3, Week 5, and then every 4 weeks until Week 49 and/or last follow-up visit;
- FSH at Week 5, Week 13, Week 25, Week 37, and Week 49 visits;
- Dihydrotestosterone at Week 5, Week 13, Week 25, Week 37, and Week 49 visits; and
- Sex hormone binding globulin at Week 13, Week 25, and Week 49 visits.

9.7. Exploratory Analyses

Overall survival: Overall survival defined as time from randomization to date of death prior to data cutoff date. Kaplan-Meier methods will be used to describe survival distributions for each treatment arm.

Pharmacogenomic analyses may be conducted to examine the contribution of genetic variance on drug response, for example, its efficacy and safety, pending availability of samples. Polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix. These analyses will be detailed in a separate statistical analysis plan and associated reports.

9.8. Interim Analyses

There will be no planned interim efficacy analysis for the study.

9.9. Sample Size

To calculate the sample size required for the primary efficacy endpoint of this study, the following assumptions have been made:

- True probabilities of sustained testosterone suppression are 94% and 96% for relugolix and leuprolide acetate, respectively;
- 2:1 randomization ratio (relugolix:leuprolide acetate); and
- Dropout rate of 15%.

The assumed probability of sustained testosterone suppression for relugolix arm is 94%. It was estimated based on the predicted dose-response relationship for the effect of relugolix on testosterone suppression in patients with prostate cancer (data from phase 2 studies C27002 and C27003). The assumed castration rate of 96% for leuprolide acetate was based on the results from degarelix phase 3 registration program [Shore, 2013].

For Evaluation Criterion 1, 610 patients in the relugolix group will provide approximately 90% power to rule out a fixed probability of sustained testosterone suppression of < 90% at a 2-sided type I error rate of 0.05.

For Evaluation Criterion 2, with the non-inferiority margin of -10% and an overall 2-sided type I error rate of 0.05, a total of approximately 915 patients (610 relugolix, 305 leuprolide acetate) will yield at least 99% power in declaring the non-inferiority of relugolix compared to leuprolide acetate.

The final analysis will be performed separately for individual evaluation criterion using data collected through 48 weeks after enrollment of approximately 915 patients.

Up to approximately 1125 patients will be randomized in order to fulfill the regulatory requirements of all participating countries. This includes approximately 90 patients from Japan (60 relugolix, 30 leuprolide acetate) and approximately 200 patients (133 relugolix, 67 leuprolide acetate) from China PR.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a US investigational new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) Part 312, subpart D, "Responsibilities of sponsors and investigators," 21 CFR Part 50, and 21 CFR Part 56, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR Part 54, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-

investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

A properly executed, written informed consent, in compliance with the Declaration of Helsinki, ICH Good Clinical Practice, US CFR for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27), and local regulations, will be obtained from each patient before entering the patient in the trial. The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

The investigator will provide copies of the signed informed consent form to each patient (or to the patient's legal representatives) and will maintain the signed original document within the patient's record file per local requirements. The investigator will also fully document the informed consent process in the patient's source records.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator Brochure, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law)

without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories:

1) Investigator's study file: The investigator's study file will contain the Investigator Brochure, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents: The required source data should include the following for each patient:
   - Patient identification (name, date of birth, gender);
   - Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
   - Participation in the study (including study number);
   - Study discussed and date of informed consent;
   - Dates of all visits;
   - Documentation that protocol-specific procedures were performed;
   - Results of efficacy parameters, as required by the protocol;
   - Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
   - Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
   - Concomitant medication (including start and end date); and
   - Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the Investigator Brochure, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.5. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on the 1572 form and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization Screening Period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.6. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability including dates and lot numbers of all study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, patient ID number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

All records must be made available to the sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

Current ICH Good Clinical Practice guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (eg, pharmacist), and the following:

- That such deliveries are recorded, for example, on the sponsor-approved drug accountability log, or other sponsor-approved pharmacy log;
- That study drug is handled and stored safely and properly in accordance with the label and the study protocol;
- That study drug is only dispensed to study patients in accordance with the protocol;

- That any unused study drug is returned to the sponsor-designated facility or standard procedures for the alternative disposition of unused study drug are followed and only after approval by the sponsor representative.

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drug to any persons except the patients in this study;
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs;
- The investigator/pharmacist will maintain a study drug inventory. The inventory will include details of material received and a clear record of when they were dispensed and to which patient;
- The investigator/pharmacist agrees to conduct a final drug supply inventory on the drug accountability record at the conclusion or termination of the study. It must be possible to reconcile delivery records with those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries must be signed by the person responsible;
- Used or unused study drug may be destroyed at the study site according to standard institutional procedures if the sponsor agrees with the procedure, and after drug accountability has been conducted by the sponsor or representative. Unused study drug not destroyed at the site must be returned to the sponsor-designated facility at the end of the study or upon expiration.

10.1.7. Inspections

During the course of the study and after study completion, it is likely that one or more quality assurance audits will be undertaken by authorized sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the protocol as well as recognized Good Clinical Practice guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed time. By signing this protocol, the investigator grants permission to the sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.8. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers (eg, http://www.clinicaltrials.gov) before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH Good Clinical Practice guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may terminate the study and send a written notice of the termination along with the reasons to the investigator. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants' interests.

If the investigator intends to terminate participation in the study, the investigator must immediately inform the sponsor and provide the reason to it.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

Ahsman M, Faessel HM, Snelder NS, MacLean D, Vis P. Modelling and simulation of oral GnRH Antagonist TAK-385 and testosterone-lowering response in Prostate Cancer Patients to Optimize Trial Design and Dose Selection. Population Analysis Group Europe. 2016; Abstr 5847. Available at: http://www.page-meeting.org/print_abstract.asp?abstract_id=5847. Accessed: 11 January 2017.

Bosland MC. Testosterone treatment is a potent tumor promoter for the rat prostate. Endocrinology. 2014 Dec;155(12):4629-33.

Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, Basaria S. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol. 2006 Aug 20;24(24):3979-83.

Brooks R. EuroQol: the current state of play. Health Policy. 1996 Jul;37(1):53-72.

Cersosimo RJ, Carr D. Prostate cancer: current and evolving strategies. Am J Health Syst Pharm. 1996 Feb 15;53(4):381-96; quiz 446-8.

Conn PM, Crowley WF Jr. Gonadotropin-releasing hormone and its analogues. N Engl J Med. 1991 Jan 10;324(2):93-103.

D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ, Lamb DS, Joseph D, Tai KH, Malone S, Ludgate C, Steigler A, Kantoff PW. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol. 2007 Jun 10;25(17):2420-5.

Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. Cancer. 1998 Oct 15;83(8):1561-6.

Efstathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, Smith MR. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. J Clin Oncol. 2009 Jan 1;27(1):92-9.

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, et al. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: EORTC; 2001.

Fayers P, Bottomley A; EORTC Quality of Life Group; Quality of Life Unit. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur J Cancer. 2002 Mar;38 Suppl 4:S125-33.

FDA Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf. Accessed: 11 January 2017.

Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol. 2007 Mar;18(3):581-92.

Firmagon (degarelix for injection). Prescribing Information. Ferring Pharmaceuticals Inc., Parsippany, NJ, USA. Revised 07/2016. Available at: http://firmagon.com/. Accessed: 12 January 2017.

Foundation for Promotion of Cancer Research. Cancer Statistics in Japan-2012. December 2012.

Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA Cancer J Clin. 2001 Jan-Feb;51(1):15-36.

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.

Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, Swinburn P, Busschbach J. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013 Sep;22(7):1717-27.

Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006 Sep 20;24(27):4448-56.

Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, Jensen JK, Olesen TK, Schröder FH. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int. 2008 Dec;102(11):1531-8.

Klotz L, O'Callaghan C, Ding K, Toren P, Dearnaley D, Higano CS, Horwitz E, Malone S, Goldenberg L, Gospodarowicz M, Crook JM. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. J Clin Oncol. 2015 Apr 1;33(10):1151-6.

Kreis W. Current chemotherapy and future directions in research for the treatment of advanced hormone-refractory prostate cancer. Cancer Invest. 1995;13(3):296-312.

Lachin J. Biostatistical Methods: The Assessment of Relative Risks. 2nd ed. Balding D, Cressie N, Fitzmaurice G, Johnstone I, Molenberghs G, Scott D, et al., editors: John Wiley & Sons, Inc.; 2010.

Limonata P, Montagnani Marelli M, Moretti RM. LHRH analogues as anticancer agents: pituitary and extrapituitary sites of action. Expert Opin Investig Drugs. 2001 Apr;10(4):709-20.

Loblaw DA, Mendelson DS, Talcott JA, Virgo KS, Somerfield MR, Ben-Josef E, Middleton R, Porterfield H, Sharp SA, Smith TJ, Taplin ME, Vogelzang NJ, Wade JL Jr, Bennett CL, Scher HI; American Society of Clinical Oncology. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive

metastatic, recurrent, or progressive prostate cancer. J Clin Oncol. 2004 Jul 15;22(14):2927-41.

Lopez AM, Pena MA, Hernandez R, Val F, Martin B, Riancho JA. Fracture risk in patients with prostate cancer on androgen deprivation therapy. Osteoporos Int. 2005 Jun;16(6):707-11.

Lupron Depot. Prescribing Information. AbbVie Inc., North Chicago, IL, USA. Revised 6/2016. Available at: http://www.lupron.com/prescribing-information.aspx. Accessed: 12 January 2017.

Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. J Urol. 2002 Sep;168(3):1005-7.

Prostap 3 DCS. Summary of Product Characteristics, Section 4.8. Takeda UK Ltd. Revised 16/03/2016. Available at: https://www.medicines.org.uk/emc/medicine/24680. Accessed: 12 January 2017.

Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS; Urologic Diseases in America Project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer. 2007 Oct 1;110(7):1493-500.

Schally AV, Coy DH, Arimura A. LH-RH agonists and antagonists. Int J Gynaecol Obstet. 1980;18(5):318-24.

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, Antonarakis ES, Beer TM, Carducci MA, Chi KN, Corn PG, de Bono JS, Dreicer R, George DJ, Heath EI, Hussain M, Kelly WK, Liu G, Logothetis C, Nanus D, Stein MN, Rathkopf DE, Slovin SF, Ryan CJ, Sartor O, Small EJ, Smith MR, Sternberg CN, Taplin ME, Wilding G, Nelson PS, Schwartz LH, Halabi S, Kantoff PW, Armstrong AJ; Prostate Cancer Clinical Trials Working Group. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016 Apr 20;34(12):1402-18.

Shore ND. Experience with degarelix in the treatment of prostate cancer. Ther Adv Urol. 2013 Feb;5(1):11-24.

Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014 Jan-Feb;64(1):9-29.

Spry NA, Kristjanson L, Hooton B, Hayden L, Neerhut G, Gurney H, Corica T, Korbel E, Weinstein S, McCaul K. Adverse effects to quality of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer. Eur J Cancer. 2006 May;42(8):1083-92.

Tolis G, Ackman D, Stellos A, Mehta A, Labrie F, Fazekas AT, Comaru-Schally AM, Schally AV. Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. Proc Natl Acad Sci U S A. 1982 Mar;79(5):1658-62.

Tombal B, Miller K, Boccon-Gibod L, Schröder F, Shore N, Crawford ED, Moul J, Jensen JK, Kold Olesen T, Persson BE. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus

leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol. 2010 May;57(5):836-42.

Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst. 2007 Oct 17;99(20):1516-24.

Waxman J, Man A, Hendry WF, Whitfield HN, Besser GM, Tiptaft RC, Paris AM, Oliver RT. Importance of early tumour exacerbation in patients treated with long acting analogues of gonadotrophin releasing hormone for advanced prostatic cancer. Br Med J (Clin Res Ed). 1985 Nov 16;291(6506):1387-8.

APPENDICES

Appendix 1. Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Note: Adapted from Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

Appendix 2. EuroQol EQ-5D-5L Questionnaire

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

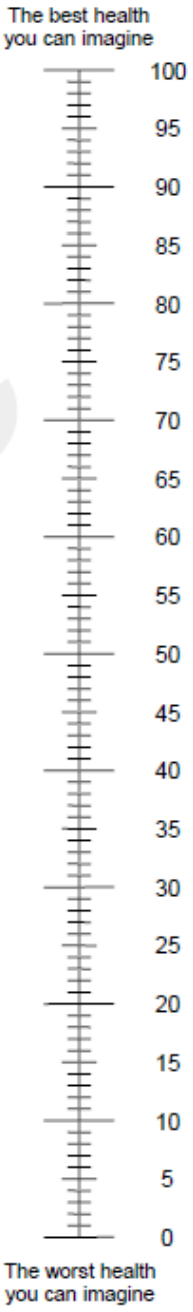
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 3. Quality of Life Questionnaire: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|

Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|

Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4. Quality of Life Questionnaire: EORTC QLQ-PR25

ENGLISH

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid: Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

ENGLISH

During the last 4 weeks:	Not at all	A little	Quite a bit	Very much
47. Has weight **loss** been a problem for you?	1	2	3	4
48. Has weight **gain** been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS:

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

Appendix 5. Adverse Event Severity Grading

When assessing adverse events, refer to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, June 14, 2010 (available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). A copy of the National Cancer Institute CTCAE table will be provided in the Study Reference Manual.

The National Cancer Institute CTCAE is a descriptive terminology that can be utilized for adverse event reporting. A grading (severity) scale is provided for each adverse event term.

Components and Organization of the National Cancer Institute CTCAE

- System Organ Class (SOC). SOC, the highest level of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy, is identified by anatomical or physiological system, etiology, or purpose (eg, SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, adverse events are listed and accompanied by descriptions of severity (grade).
- CTAE Terms. Each CTCAE term is a MedDRA LLT (Lowest Level Term).
- Definitions. A brief definition is provided to clarify the meaning of each adverse event term.
- Grades. Grade refers to the severity of the adverse event. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each adverse event based on this general guideline:
    - Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
    - Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
    - Grade 4 Life-threatening consequences; urgent intervention indicated; and
    - Grade 5 Death related to adverse event.

      A semi-colon indicates “or” within the description of the grade. A single dash (-) indicates a grade is not available. Not all grades are appropriate for all adverse events. Therefore, some adverse events are listed with fewer than 5 options for grade selection.
- Grade 5. Grade 5 (Death) is not appropriate for some adverse events and therefore is not an option.

Appendix 6. Guidelines for Elevations in Hepatic Enzymes

Study drug treatment should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld, even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests[a]
If AST or ALT ≥ 3 x ULN **and** total bilirubin > 2 x ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 x ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

- Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever);
- Prior and concurrent disease or illnesses;
- Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents;
- Prior and concurrent use of alcohol, recreational drugs, and special diets;
- Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms;
- Physical examination.

Recommended tests:

Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist.

- Repeat liver tests as per Appendix Table 1[a];
- Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests;
- Complete blood count with differential to assess for eosinophilia;
- Serum acetaminophen (paracetamol) concentration;
- Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus;
- Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc;
- Serology for celiac disease;
- Appropriate liver imaging; and
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

Abbreviations: INR, international normalized ratio

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

CLINICAL STUDY PROTOCOL

Study Title:	HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3201
Indication:	Advanced Prostate Cancer
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
IND Number:	118736
EudraCT Number:	2017-000160-15
Version / Effective Date:	Version 02 Jan 2018
Study Medical Monitor:	PPD

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Myovant Sciences GmbH, and is provided to you in confidence as an investigator, potential investigator or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Myovant Sciences GmbH, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SPONSOR SIGNATURE PAGE

HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer

Protocol Number: MVT-601-3201

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

02-Jan-2018

Date

02-JAN-2018

Date

02JAN2018

Date

02 Jan 2018

Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	**Signature**
Date	**Site**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
3-M	3-month
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
$AUC_{0-\tau}$	area under the concentration-time curve from time 0 to the end of the dosing interval
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DHT	dihydrotestosterone
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation of Research and Treatment of Cancer
EOT	end of treatment
EuroQol EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Questionnaire
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HbA1c	hemoglobin A1c
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
ICH	International Conference on Harmonization
ID	identification
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat (population)
IWRS	interactive voice/web recognition system
LH	luteinizing hormone
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

Term	Explanation
NOAEL	no-observed-adverse-effect-level
NYHA	New York Heart Association
Obs	observed
PK	pharmacokinetics
PLD	phospholipidosis
PSA	prostate-specific antigen
Q12W	once every 12 weeks
Q4W	once every 4 weeks
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QTc corrected using Fridericia's formula
SHBG	sex hormone binding globulin
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States

1. PROTOCOL SYNOPSIS

Study Title	HERO: A Multinational Phase 3, Randomized, Open-label, Parallel-group Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer
Protocol Number	MVT-601-3201
Location	Multinational, including North and South America, Europe, and Asia-Pacific
Study Centers	Approximately 200 sites
Study phase	Phase 3
Target Population	Men aged 18 or older diagnosed with androgen-sensitive advanced prostate cancer who are candidates for at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer and who are not be candidates for surgical therapy. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy.
Number of Patients Planned	Approximately 915 total patients
Study Objectives	Primary: • To evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) in men with androgen-sensitive advanced prostate cancer. Secondary: • To evaluate the time course and change in serum testosterone during treatment with relugolix; • To evaluate the time course and magnitude of prostate-specific antigen (PSA) reduction during treatment with relugolix; • To evaluate testosterone recovery following discontinuation of relugolix; • To evaluate quality of life using validated patient-reported outcome instruments; • To evaluate the safety of relugolix 120 mg once daily in men with androgen-sensitive advanced prostate cancer; • To evaluate the effect of relugolix and leuprolide acetate on endocrine pharmacodynamic parameters; • To collect relugolix plasma concentration data to further evaluate relugolix population pharmacokinetics (PK) and the relationship between relugolix exposure and serum testosterone; and • To characterize the relugolix plasma PK parameters in a subset of patients from China (if enrolled) and Japan; and • To describe the time course and magnitude of PSA progression and

	development of castration resistant prostate cancer during treatment with relugolix. Exploratory: • To explore the overall survival of patients treated with relugolix; and • To explore the contribution of genetic variance on drug response.

Study Design

The HERO study is a phase 3 multinational randomized, open-label, parallel-group study to evaluate the safety and efficacy of relugolix in patients with androgen-sensitive advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy. Relugolix is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist that lowers testosterone by inhibiting pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Relugolix 120 mg orally once daily or leuprolide acetate depot suspension, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China), every 3-months (3-M) will be administered to patients with prostate cancer who require androgen deprivation therapy. This study will evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) for 48 weeks in patients with androgen-sensitive advanced prostate cancer.

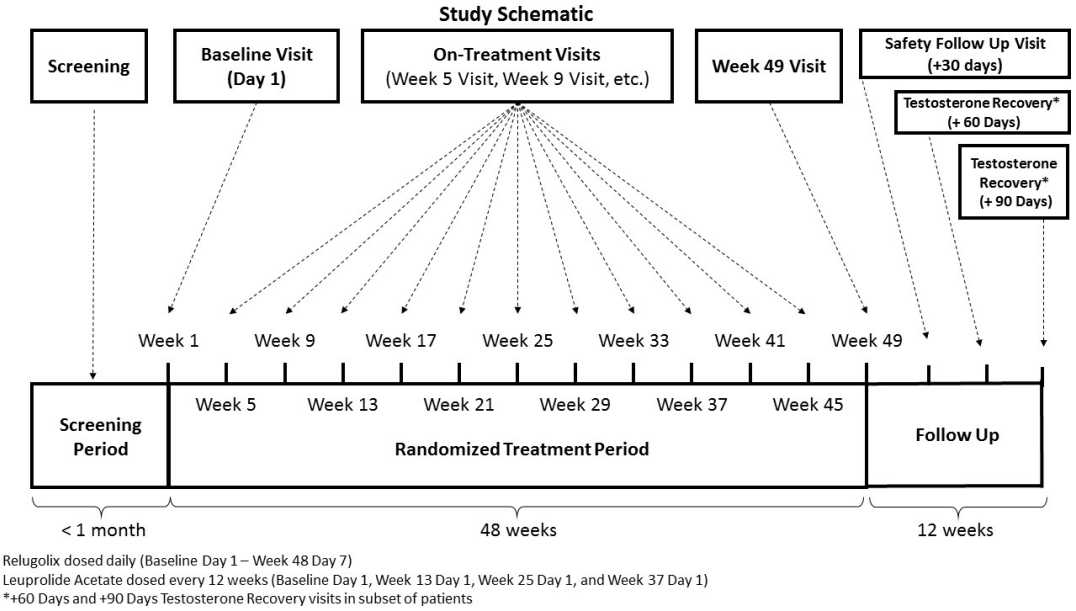
To be eligible for the study, a patient must be, in the opinion of the investigator, a candidate for at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer and must not be a candidate for surgical therapy. Eligible patients include those with evidence of biochemical relapse (rising PSA) following local primary intervention with curative intent, newly diagnosed metastatic disease (excluding metastases to the brain), and/or advanced localized disease. Patients may receive radiotherapy, cryotherapy or high frequency ultrasound no sooner than 2 months after initiation of androgen deprivation therapy. Patients may be included if they have not previously received androgen deprivation therapy for more than 18 months, and if the androgen deprivation therapy was completed at least 3 months prior to the baseline visit. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy. Baseline serum testosterone must be ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L) to be enrolled.

Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg once daily following a loading dose of 360 mg on Day 1 or 3-M depot of leuprolide acetate 22.5 mg (or 11.25 mg in Japan, Taiwan, and China). After randomization, patients on the leuprolide acetate arm may receive an antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator. Randomization will be stratified by geographic region, presence of metastatic disease, and age.

Approximately 915 patients will be enrolled in this study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region. The study includes a Screening Period of up to 28 days, a Treatment Period of 48 weeks, and a Follow-up Period of up to 90 days. Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed. Eligible patients will receive study treatment for 48 weeks. During that time, testosterone and PSA will be assessed monthly and patient-reported outcomes (European Organisation of Research and Treatment of Cancer [EORTC] QLQ-C30, European Quality of Life 5-Dimesion 5-Level questionnaire [EuroQol EQ-5D-5L]) will be

assessed approximately every 3 months during the Treatment Period and more frequently during the Follow-up Period. Additional serum endocrine evaluations will include: LH, FSH, dihydrotestosterone, and sex hormone binding globulin. Relugolix PK samples will be collected throughout the study. Full PK profiles will be determined in a subset of patients in China (if enrolled) and Japan. Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECG), and visual acuity tests.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (testosterone level ≤ 50 ng/dL [1.7 nmol/L]), should remain on study and may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide. For patients requiring other systemic antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.



Relugolix dosed daily (Baseline Day 1 – Week 48 Day 7)
Leuprolide Acetate dosed every 12 weeks (Baseline Day 1, Week 13 Day 1, Week 25 Day 1, and Week 37 Day 1)
*+60 Days and +90 Days Testosterone Recovery visits in subset of patients

Inclusion/Exclusion Criteria

Inclusion Criteria

All of the following inclusion criteria must have been met prior to randomization unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a male aged 18 years or older on the day of signing and dating the informed consent form;
3. Has histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate;
4. Is a candidate for, in the opinion of the investigator, at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer

with one of the following clinical disease state presentations:

a. Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, such as surgery, radiation therapy, cryotherapy, or high-frequency ultrasound and not a candidate for salvage treatment by surgery; or

b. Newly diagnosed androgen-sensitive metastatic disease; or

c. Advanced localized disease unlikely to be cured by - local primary intervention with either surgery or radiation with curative intent;

Note: radiotherapy, cryotherapy, or high frequency ultrasound are allowed after 2 months of androgen deprivation therapy.

5. Has a serum testosterone at the Screening visit of ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L);
6. Has a serum PSA concentration at the Screening visit of > 2.0 ng/mL (2.0 µg/L), or, when applicable, post radical prostatectomy of > 0.2 ng/mL (0.2 µg/L) or post radiotherapy, cryotherapy, or high frequency ultrasound > 2.0 ng/mL (2.0 µg/L) above the post interventional nadir;
7. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at initial screening and at baseline (refer to Appendix 1);
8. Is a male patient who, even if surgically sterilized (ie, status post vasectomy):

   a. Agrees to use a male condom if having sex with a woman of childbearing potential or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or

   b. Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception;

9. Must agree not to donate sperm from first dose of study drug through 4 months after the last dose of study drug;
10. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

1. In the investigator's opinion, is likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating androgen deprivation therapy;
2. Previously received GnRH analog or other form of androgen deprivation therapy (estrogen or antiandrogen) for > 18 months total duration. If androgen deprivation therapy was received for ≤ 18 months total duration, then that therapy must have been completed at least 3 months prior to baseline. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot;
3. Previous systemic cytotoxic treatment for prostate cancer (e.g. taxane-based regimen);
4. Metastases to brain per prior clinical evaluation;

5. *Removed;*
6. Scheduled for major surgery after baseline;
7. History of surgical castration;
8. Active malignancy beyond prostate cancer ***with the exception*** of any of the following:
   - Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ carcinoma of any type;
   - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for ≥ 2 years;
   - Any other cancer from which the subject has been disease-free for ≥ 5 years;

   The medical monitor should be contacted for any questions regarding this exclusion criterion;
9. Abnormal laboratory values at the Screening visit that suggest a clinically unstable underlying disease, or the following laboratory values:
   a. Serum gamma-glutamyl transferase > 2.0 x upper limit of normal (ULN);
   b. Serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > ULN;
   c. Total bilirubin > ULN (unless secondary to Gilbert's syndrome or the pattern is consistent with a diagnosis of Gilbert's syndrome);
   d. Serum creatinine > 2.0 mg/dL (176.8 µmol/L);
   e. Platelets < 100 x 10^3/µL or history of bleeding disorder;
   f. Hemoglobin < 10.0 g/dL (100 g/L);
   g. Leukocytes (WBC) < 3 x 10^3/µL (3 GI/L); or
   h. Absolute neutrophil count < 1.5 x 10^3/µL (1.5 GI/L);
10. Hemoglobin A1c (HbA1c) > 10% in patients previously diagnosed with diabetes mellitus. HbA1c > 8% in patients whose diabetes mellitus is previously undiagnosed. (Excluded patients may be rescreened after referral and evidence of improved control of their condition);
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (hepatitis A virus immunoglobulin M [IgM] positive), hepatitis B (hepatitis B virus surface antigen [HBsAg] positive), or hepatitis C (hepatitis C virus [HCV] antibody positive, confirmed by HCV ribonucleic acid);
12. Known human immunodeficiency virus infection;
13. Any of the following within 6 months before Baseline Day 1:
    a. Myocardial infarction;
    b. Unstable angina;
    c. Unstable symptomatic ischemic heart disease;
    d. New York Heart Association (NYHA) class III or IV heart failure;
    e. Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events);

f. Any other significant cardiac condition (e.g., pericardial effusion, restrictive cardiomyopathy, severe untreated valvular stenosis, or severe congenital heart disease);

14. The following ECG abnormalities are excluded:

    a. ECG evidence of acute ischemia;

    b. Q-wave infarction, unless identified 6 or more months before the Screening visit;

    c. QT interval corrected for heart rate (QTc) > 470 msec, measured by Fridericia's formula [QTcF = QT/(RR^0.33)]. If the QTc is prolonged in a patient with a pacemaker, the patient may be enrolled in the study if confirmed by the medical monitor; or

    d. Congenital long QT syndrome;

    e. Active conduction system abnormalities. Examples of active conduction system abnormalities include the following:

    - Mobitz II second degree heart block without a permanent pacemaker in place;
    - Third degree heart block without permanent pacemaker in place;
    - Untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    - Clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes;
    - Uncontrolled atrial fibrillation (patients with chronic stable atrial fibrillation on stable anticoagulant therapy or patients with stable cardiac rhythm controlled by a pacemaker are allowed);

    The following exceptions are allowed: First degree atrioventricular (AV) block, second degree AV block Type 1 (Mobitz Type 1/Wenckebach type), or right bundle branch block.

15. Uncontrolled hypertension despite appropriate medical therapy (sitting blood pressure of greater than 160 mmHg systolic and/or 100 mmHg diastolic at 2 separate measurements no more than 45 minutes apart during the Screening visit). Patients may be re-screened after referral and further management of hypertension;

16. Hypotension, as indicated by systolic blood pressure < 84 mmHg on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming upright position;

17. Bradycardia as indicated by a heart rate of < 45 beats per minute on the ECG at the Screening or Baseline Day 1 visit;

18. Treatment with any investigational product within 28 days or 5 half-lives (whichever is longer);

    Exception: treatment for prostate cancer with any investigational products where the mechanism of action is testosterone lowering. In this circumstance, there must be a minimum 12-month treatment free interval;

19. *Removed*;

20. Previous treatment with relugolix in a clinical study;

21. Patient is a study site employee or is a primary family member (spouse, parent, child, or

sibling) of a site employee involved in the conduct of the study; 22. Known gastrointestinal disease or procedure that could interfere with the oral absorption or tolerance of relugolix, including inability to swallow whole tablets or conditions that may interfere with absorption at the level of the small intestine. Examples of such conditions include but are not limited to Crohn's disease, gastric bypass, active peptic ulcer disease, and gastrectomy. The medical monitor should be contacted for any questions regarding this exclusion criterion; 23. Use or planned use of any medication listed in the prohibited medications table (see Section 5.10.1) without the appropriate washout period; 24. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation; 25. Has a prior (within 1 year of the Screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form [eCRF]); 26. Any other medical or psychiatric condition that, in the opinion of the investigator, would interfere with completion of treatment according to this protocol. 27. Weight ≥ 400 pounds (181 kg) or has a body mass index ≥ 50;	
Dose and Route of Administration	Test Product Relugolix 120 mg tablet strength will be available as immediate-release film-coated tablets, and 1 tablet (120 mg) will be administered once daily following an oral loading dose of 360 mg (three 120-mg tablets) on Day 1. These tablets will be presented in 45-tablet bottles and dispensed to patients every 4 weeks at scheduled study visits. All protocol-specific inclusion criteria and none of the exclusion criteria must be met and documented prior to study drug administration. Study drug will be dispensed only to eligible patients who are under the supervision of the investigator or identified subinvestigator(s). Reference Product Leuprolide acetate, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China), 3-M depot will be administered per the approved dose and method of dosing in the region where the patient is enrolled. Leuprolide acetate 3-M depot injection will be administered on Day 1 (with an antiandrogen of choice, if indicated according to the investigator, for the first 4 weeks or longer), then at 12-week intervals thereafter for 48 weeks. Preparation of the depot injection and administration should follow the instructions provided by the manufacturer.
Duration of Treatment	The duration of treatment will be 48 weeks. The last dose of leuprolide acetate 3-M depot will be administered at the Week 37 visit.
Criteria for Evaluation	The following treatment arms will be evaluated after 48 weeks of study treatment: • Arm A: Oral relugolix 120 mg once daily following a loading dose of

	360 mg (three 120-mg tablets) on Day 1. • Arm B: Leuprolide acetate 3-M depot injection, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China). Primary Endpoint • Sustained castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). Secondary Endpoints • Describe effects on serum testosterone: o Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4, prior to dosing on Week 3 Day 1; o Profound castration rate defined as the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) while on study treatment from Week 25 Day 1 through Week 49 Day 1; o Time to testosterone recovery in approximately 100 patients randomized to relugolix and approximately 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of leuprolide acetate 3-M depot); • Describe effects on PSA: o Proportion of patients with confirmed PSA response by Prostate Cancer Clinical Trials Working Group 3 guidelines at the Week 3 and Week 5 visits [Scher, 2016]; o Proportion of patients with PSA concentration < 0.2 ng/mL (0.2 µg/L) at the Week 25 visit; • Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable during the Follow-up and/or at End of Treatment visits; • Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as the EuroQol EQ-5D-5L questionnaire, at regular intervals during treatment, and as applicable during the Follow-up visits; • Incidence of adverse events; • Incidence of abnormalities in clinical laboratory data; • Endocrine marker effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for: o LH at the Day 4, Week 5, Week 25, and Week 49 visits; o FSH at the Day 4, Week 5, Week 25, and Week 49 visits; o Dihydrotestosterone at the Week 5, Week 25, and Week 49 visits; and o Sex hormone binding globulin at the Week 5, Week 25, and Week 49 visits; • Predose relugolix plasma concentrations;

	• Single and repeat-dose plasma relugolix PK parameters such as maximum plasma concentration (C_{max}), area under the concentration-time curve from time 0 to the end of the dosing interval ($AUC_{0-\tau}$), and time to maximum plasma concentration (t_{max}) in a subset of patients from China (if enrolled) and Japan during the Day 1 visit. • Time-to PSA progression; • Proportion of patients with confirmed PSA progression among those who have achieved sustained testosterone suppression during the 48-week treatment. <u>Exploratory Endpoints</u> • Overall survival defined as time from randomization to date of death prior to data cutoff date; and • The presence of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix. These will be evaluated in a subset of patients.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) population defined as all randomized patients who have taken at least one dose of study treatment. Randomization will be stratified by geographic region (North and South America versus Europe versus Asia and Rest of World), presence of metastatic disease on baseline imaging (yes versus no), and age (≤ 75 years old versus > 75 years old). The 2-sided type I error rate for this study is 0.05.

Primary Efficacy Endpoint:

The primary efficacy endpoint is the sustained castration rate defined as the cumulative probability of achieving testosterone suppression to castrate levels of ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). This probability will be estimated for each treatment group using the Kaplan-Meier method with the confidence interval calculated using the exponential Greenwood formula via log-log transformation of the survival function. Patients who discontinue treatment prior to observing a testosterone level > 50 ng/dL (1.7 nmol/L) will be censored at the last testosterone assessment prior to discontinuation. Detailed censoring rules will be prespecified in the statistical analysis plan.

There are 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit:

- Evaluation Criterion 1: to determine whether the sustained castration rate for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression to castrate levels in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion.
- Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot as assessed by the cumulative probability of sustained testosterone suppression to castrate levels. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression to castrate levels between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.

The 2-sided type I error rate will be 0.05 for each individual evaluation criterion.

Secondary Efficacy Endpoints:

1. Castration rate: the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4, and prior to dosing on Week 3 Day 1;
2. Profound castration rate: the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) from Week 25 through Week 49;
3. PSA response rate: proportion of patients with a ≥ 50% decrease in PSA from baseline at Week 3 and confirmed at Week 5;
4. Undetectable PSA rate: proportion of patients with PSA concentration < 0.2 ng/mL (0.2 µg/L) at the Week 25 visit;
5. Time to testosterone recovery in approximately 100 relugolix-treated and approximately 50 leuprolide acetate-treated patients who complete 48 weeks of treatment and do not start alternative androgen deprivation therapy within 12 weeks after the last dose of relugolix or within 24 weeks following the last received injection of leuprolide acetate. Kaplan-Meier methods will be used to describe survival distributions;
6. Quality of Life: absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-

treatment-related symptom subdomains, at regular intervals during treatment, and as applicable at the Follow-up and/or End-of-Study visits will be presented. Additionally, absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as EQ-5D-5L, at regular intervals during treatment, and as applicable during the Follow-up visits will be presented. Change from baseline will be analyzed using mixed-model repeated measures methodology;
7. Time to PSA progression;
8. Proportion of patients with confirmed PSA progression among those who have achieved sustained testosterone suppression during the 48-week treatment period.

Exploratory Endpoints:

1. Overall survival: Overall survival defined as time from randomization to date of death prior to data cutoff date. Kaplan-Meier methods will be used to describe survival distributions;
2. The effect of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or drug metabolizing enzymes and transporter proteins on the efficacy and safety of relugolix will be described in a separate statistical analysis plan.

The methods and procedures needed to maintain a study-wide 2-sided type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

Pharmacokinetics

Relugolix plasma concentrations will be summarized and described using population PK methods. Plasma PK parameters in a subset of patients from China (if enrolled) and Japan will be determined using noncompartmental methods.

Safety

Safety assessments, including adverse events, vital signs, clinical laboratory tests, and ECGs, will be summarized for the treatment-emergent period. The treatment-emergent period is defined as the time from first dose of study drug through 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last dose of leuprolide acetate. Safety analyses will be based on all randomized patients who receive any amount of study drug (Safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher-level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive rather than inferential statistics will be used. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of baseline versus post baseline results will be produced.

An independent Data and Safety Monitoring Board will monitor all available safety data on a periodic basis. The roles and responsibilities of the Data and Safety Monitoring Board will be described in detail in a separate charter.

Sample Size

To calculate the sample size required for the primary efficacy endpoint of this study, the following assumptions have been made:

- True probabilities of sustained castration rates are 94% and 96% for relugolix and leuprolide acetate, respectively;
- 2:1 randomization ratio (relugolix:leuprolide acetate);
- Dropout rate of 15%.

For Evaluation Criterion 1, 610 patients in the relugolix group will provide approximately 90% power to rule out a fixed probability of sustained testosterone suppression of ≤ 90% at a 2-sided type I error rate of 0.05.

For Evaluation Criterion 2, with the non-inferiority margin of -10% and a 2-sided type I error rate of 0.05, a total of approximately 915 patients (610 relugolix, 305 leuprolide acetate) will yield at least 99% power in declaring the non-inferiority of relugolix compared to leuprolide acetate.

The primary analysis of the primary efficacy endpoint will be performed after at least 915 patients have had the opportunity to complete 48 weeks of study drug treatment. The evaluation criteria used for the primary efficacy endpoint assessment will be determined by regional regulatory requirements and will be prespecified in separate regional statistical analysis plans.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3201

Period	**Screening Visit**	**Treatment Period Visits**														**Follow-up[a,c]**		
																Safety[b]	**Testosterone Recovery**	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2[q]**	**Wk 3**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17 and 21**	**Wk 25**	**Wk 29 and 33**	**Wk 37**	**Wk 41 and 45**	**Wk 49[e]**	**Un-scheduled**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**		**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**		**±2 days**			**± 7 days**										**± 7 days**		
Informed Consent[f]	X																	
Inclusion/ Exclusion Criteria	X	X																
Study Drug Dispensation: Relugolix		X				X	X	X	X	X	X	X	X		X[r]			
Study Drug Administration: Relugolix Once Daily		X	X Patients will receive a single loading dose of oral relugolix 360 mg on Day 1 in the clinic; Starting on Day 2, patients will take oral relugolix 120 mg once daily												X[r]			
Study Drug Administration: Leuprolide Acetate 3-M Depot		X						X		X		X			X[r]			
Phone call prior to visit and study drug accountability[d]						X	X	X	X	X	X	X	X	X	X[r]			
Demographics	X																	
Medical History (including detailed prostate cancer history)	X	X																

Period	Screening Visit	Treatment Period Visits														Follow-up[a,c]		
																Safety[b]	Testosterone Recovery	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2[q]**	**Wk 3**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17 and 21**	**Wk 25**	**Wk 29 and 33**	**Wk 37**	**Wk 41 and 45**	**Wk 49[e]**	**Un-scheduled**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**		**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**		**±2 days**			**± 7 days**										**± 7 days**		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X	X
Weight, BMI	X	X						X		X				X	X[r]	X		
Height	X														X[r]			
12-lead ECG[g]	X	X				X		X		X				X	X[r]	X		
ECOG Performance Assessment	X	X								X				X	X[r]	X		
Complete Physical Exam and Visual Acuity[h]	X									X				X	X[r]			
Symptom Based Physical Exam		X				X	X	X	X		X	X	X		X[r]	X	X	X
Abdominopelvic CT or MRI and Bone Scan[i]	X														X[r]			
EuroQol EQ-5D-5L Health Questionnaire		X				X		X		X		X		X	X[r]	X	X	X
EORTC-QLQ-PR25 and EORTC-QLQ-C30 Quality of Life Questionnaires		X				X		X		X		X		X	X[r]	X	X	X
Adverse Events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X	X
Hematology	X	X						X		X		X		X	X[r]	X		
Chemistry	X	X				X		X		X		X		X	X[r]	X		

Period	Screening Visit	Treatment Period Visits														Follow-up[a,c]		
																Safety[b]	Testosterone Recovery	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2[q]**	**Wk 3**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17 and 21**	**Wk 25**	**Wk 29 and 33**	**Wk 37**	**Wk 41 and 45**	**Wk 49[e]**	**Un-scheduled**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**		**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**		**±2 days**			**± 7 days**										**± 7 days**		
Lipid & HbA1c[k]	X									X				X	X[r]	X		
PSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X	X
Serum Testosterone	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[r]	X	X	X
LH/FSH		X	X			X				X				X	X[r]	X	X	X
SHBG/DHT		X				X				X				X	X[r]			X
Blood Sample for Relugolix PK[m,n]		X[m,n]	X[n]	X[n]		X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[r]			
Blood Sample for DNA[o]		X													X[r]			
Health Status Survey[p]														X	X[r]			

Abbreviations: 3-M, 3-month; BMI, body mass index; CT, computed tomography; DHT, dihydrotestosterone; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; EuroQol EQ-5D-5L, European Quality of Life 5-Dimension 5-Level; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; LH, luteinizing hormone; MRI, magnetic resonance imaging; PK, pharmacokinetics; PSA, prostate-specific antigen; SHBG, sex hormone binding globulin

a. The study day in which the Follow-up visit occurs is not specified in the table because these visits occur relative to when the patient takes his last dose of study drug. The End of Treatment (EOT) is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.
b. May occur earlier for patients who are starting alternative androgen deprivation therapy, or do not complete 12 weeks of study treatment. Adverse events, serious adverse events, and concomitant medications should continue to be collected and recorded through 30 days after the End of Treatment. All other study procedures should be completed before the start of alternative androgen deprivation therapy.
c. Patients who have started alternative androgen deprivation therapy will not participate in the 60- and 90-day Follow-up visits. For approximately 100 patients receiving relugolix and approximately 50 patients receiving leuprolide acetate who complete 48 weeks of study drug treatment and, in the opinion of the investigator, can remain off androgen deprivation therapy for 90 days will be included in the testosterone recovery 60- and 90-day Follow-up visits.
d. For patients assigned to the relugolix treatment arm, the patient should be called 7 days before their next visit to check on compliance with their study medication. Study drug accountability will be conducted at visits and results will be recorded as the primary source of study drug accountability.
e. If patient terminates early from study treatment, the patient should be asked to come in as soon as possible and complete this visit.
f. The informed consent form must be signed before any study-mandated procedures are performed.

g. 12-lead ECGs should be read locally by a qualified physician.
h. A complete physical examination should be performed. Visual acuity will be evaluated by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment. Patients whose presenting visual acuity score is 90 or lower at the screening visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, i.e., an ophthalmologist or an optometrist. Any findings (i.e., diagnoses) from the eye examination should be recorded as medical history. Patients whose presenting visual acuity score at Week 25, Week 49, or Early Termination has decreased by 10 or more points from the screening visit should be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor
i. An abdominopelvic CT or MRI and a bone scan should be performed and read locally to determine the presence of metastatic disease within 60 days prior to randomization. However, if CT or MRI demonstrates presence of metastatic disease, a bone scan is not required. If metastatic disease is not present on CT or MRI, then a bone scan is also required.
j. Collect serious adverse event information from the time of signed informed consent through the Safety Follow-up Visit, which is through 30 days after the last dose of relugolix or 12 weeks and 30 days after the last injection of leuprolide acetate, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit (or from the time of signed informed consent if event was related to a screening study procedure through approximately 30 days after the last dose of relugolix or 12 weeks and 30 days after the last injection of leuprolide acetate, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first.
k. Blood samples must be obtained fasting; nothing to eat or drink (other than water) for at least 9 hours prior to obtaining the sample.
l. All testosterone samples obtained from Week 5 and beyond are to be collected during a ± 7-day window.
m. Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose, approximately 24 hours after the previous dose. Patients may be dosed in the clinic at these visits, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing.
n. A subset of patients from China (if enrolled) and Japan will have additional samples collected predose, and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Day 1 and Week 2 visits. Patients will be dosed in the clinic at these visits. The dose will be administered at least 2 hours after food; food should be withheld for 1 hour after dosing. A predose sample (approximately 24 hours after the previous dose) also will be collected at the Day 4 visit. Patients may be dosed in the clinic at the Day 4 visit, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing.
o. The blood sample for DNA should be collected at the Baseline Day 1 visit, but may be collected at any visit if it is missed at that visit.
p. During the final weeks prior to database lock, sites will be asked to contact all study participants or their immediate family regarding the current health status of previously enrolled/completed study patients.
q. Week 2 visit will only occur for patients who are part of the Japan or China subset for PK analysis.
r. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.

2. INTRODUCTION

2.1. Prostate Cancer

Prostate cancer is the most prevalent form of cancer in men and the second leading cause of death due to cancer in men in the US [Greenlee, 2001] and Europe [Ferlay, 2007]. The median age of diagnosis is 70 years, and diagnosis before the age of 40 years is rare [Cersosimo, 1996]. In Japanese men, prostate cancer was the fourth leading cancer diagnosis in 2007 [Foundation for Promotion of Cancer Research, 2012]. The incidence of invasive prostate cancer increases with age; a clear increase is seen among men aged 60 years or older [Siegel, 2014].

If prostate cancer is diagnosed at a stage where it is confined to the prostate gland and immediate surroundings, it is generally treated by surgical removal of the prostate gland, or prostatectomy, or with radiation. Often, these procedures are successful in curing men of their disease. Men whose disease progresses after prostatectomy or radiation are said to have advanced prostate cancer. Advanced prostate cancer is defined as either: PSA biochemical relapse following primary surgical or radiation therapy of curative intent; newly diagnosed metastatic prostate cancer; or advanced localized disease for which immediate radiation or surgical therapy is not indicated. The cure rate following surgery, depending on the stage of the cancer, is about 70% overall and, following radiation, about 50% to 60%.

Approximately 25% to 30% of men will, therefore, progress to advanced disease, excluding those with metastatic disease at the time of diagnosis. Androgens, such as testosterone and its more potent metabolite dihydrotestosterone, are strong tumor promoters for prostate cancer [Bosland, 2014]. Through the androgen receptor, they synergistically augment the effect of other tumor promoters or carcinogens. Although prostate cancer is driven by presumed mutations in other tumor promoting pathways and/or by translocations leading to aberrant activation of the androgen receptor pathway, most early-stage prostate cancer cells remain either sensitive to or dependent upon circulating androgens. Thus, for more than 60 years, androgen deprivation therapy with surgical or medical castration has been the foundational therapy for either advanced inoperable or metastatic cancer. Increasingly, androgen deprivation therapy is used earlier as a neoadjuvant/adjuvant treatment to radiation therapy or for biochemical or clinical relapse after local therapies of curative or palliative intent. More than 80% of men with progressive or advanced disease initially respond to androgen deprivation therapy with varying degrees of tumor regression or stabilization [Kreis, 1995]. The duration and depth of response to androgen deprivation therapy is presumably dependent on the underlying tumor biology and burden. Thus, patients with metastases respond for an average of 2 years before any biochemical evidence of castration resistance occurs. By contrast, patients with biochemical-only evidence of progressive disease may respond to androgen deprivation therapy for 5 years or more [Klotz, 2015].

Currently, most patients in developed countries receive medical rather than surgical castration. GnRH (or LH-releasing hormone) agonists (ie, long-acting leuprolide acetate depot injections) are the current mainstay of medical castration, causing long-term desensitization and down regulation of the hypothalamic-pituitary gonadal axis. One disadvantage of the agonist form of GnRH is the initial stimulation of the axis lasting 1 to 3 weeks that occurs prior to desensitization. This results in a rise in LH and testosterone levels and an increase in clinical symptoms. In addition, at the time of repeat injection of GnRH agonist depot, microsurges of

LH and testosterone may occur, although the apparent incidence is low [Klotz, 2008]. The initial flare response may be managed with simultaneous antiandrogen administration, such as with bicalutamide.

Recently, GnRH antagonists, in particular degarelix, [Firmagon, 2016], have become available as an alternative form of medical castration. Degarelix, an injectable peptide, has been approved in some countries for the treatment of patients with advanced prostate cancer. As a GnRH antagonist, degarelix achieves medical castration and PSA response with no initial agonist activity within the first 1 to 2 weeks of administration, and effectively can obviate the need for concomitant antiandrogen treatment. Post-hoc analyses of degarelix trials [Tombal, 2010] suggest that it may have additional advantages regarding disease response or secondary relapse; however, such differences require confirmation in prospective studies. Because of the need for monthly depot injections, with large volumes and accompanying local reactions, the use of degarelix in clinical practice has remained low.

Relugolix, previously known as TAK-385, is a potent and highly selective oral small molecule antagonist for the human GnRH receptor. For patients, relugolix may offer the advantages conferred by a direct receptor antagonist, including a more rapid onset of action and the absence of clinical flare or worsening of symptoms from the initial rise in androgens caused by GnRH agonists, as well as having the added convenience and relative comfort of oral dosing.

2.2. Relugolix

2.2.1. Indication

Relugolix is being developed as a once daily oral medication for the treatment of advanced prostate cancer. The proposed dose of relugolix is 120 mg administered orally once daily following a loading dose of 360 mg (three 120-mg tablets) on Day 1.

2.2.2. Pharmacology

Relugolix is an orally-active, potent, highly-selective, high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes the human GnRH receptors present on the gonadotrophin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in testosterone in men and estradiol and progesterone levels in women. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 µg·hr/mL, which is ~51 times higher than the estimated exposure (area under the concentration-time curve [AUC]) in men receiving 120 mg once daily (0.469 µg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 µg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥ 100 mg/kg (estimated C_{max} of 4.0 µg/mL), but did not prolong the QT interval in a human Thorough QT study at doses up to 360 mg (C_{max} of 0.181 µg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and 3 phase 2 studies have been completed. In addition, 6 clinical studies evaluating relugolix are ongoing, including 2 phase 1 studies, 2 phase 2 studies in men with prostate cancer (US and Europe), and 2 phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least one dose of relugolix, including 158 women receiving relugolix 40 mg once daily for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of testosterone in male subjects and estradiol in female subjects. After oral

administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The PK and pharmacodynamics of relugolix have been evaluated, and appear to be similar in Western and Asian volunteers, despite the lower mean body mass index observed in Asian volunteers.

A relative bioavailability and food effect study was conducted using the global phase 3 prostate cancer formulation of 120 mg relugolix. After administration with a high-fat, high-calorie breakfast, the C_{max} and AUC of relugolix were reduced, on average, by 21.4% and 18.8%, respectively.

In the phase 1 study C27001, serum LH, FSH, dihydrotestosterone, and testosterone concentrations were determined in healthy men following single and multiple oral doses of relugolix or placebo for up to 28 days. Loading doses of ≥ 160 mg on Day 1 were used to shorten the time to testosterone suppression. Relugolix caused an immediate and effective suppression of LH, FSH, and testosterone. After 14 days of once daily dosing, mean LH and serum testosterone concentration profiles were similar for the 40, 80, and 180 mg relugolix dose cohorts. LH, FSH, and testosterone concentrations began decreasing 2 to 6 hours postdose on Day 1 and remained suppressed through Day 14. However, the relugolix once daily maintenance dose was a major determinant of sustained testosterone suppression. Profound castration (defined as average testosterone levels < 20 ng/dL or 0.7 nmol/L) was achieved with 40, 80, or 180 mg once daily for 14 days; however, 20 mg once daily was insufficient in maintaining adequate suppression of serum LH and testosterone concentration levels during the second week.

In healthy, older men receiving 14 or 28 days of dosing, effective castration was consistently achieved over 14 and 28 days dosing at daily doses of 40 to 180 mg (14 days) and 80 to 160 mg (28 days). Use of a loading dose for up to 3 days (or once daily doses of ≥ 160 mg) resulted in castration levels of testosterone (< 50 ng/dL or 1.7 nmol/L) within 24 to 48 hours. Results obtained after 28 days of dosing suggested that the likely minimal, fully effective maintenance dose for sustained castration would be relugolix ≥ 80 mg once daily. Doses of 80 mg and 120 mg were moved forward into phase 2 development.

Relugolix is to be administered in the fasted state (at least 1 hour before or 2 hours after a meal), as food decreases the extent of relugolix absorption by approximately 20%. The exposure of relugolix is increased by inhibitors of P-glycoprotein up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 (CYP) 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong QTc at single doses of 60 or 360 mg.

2.2.4.2. Clinical Studies in Men with Prostate Cancer

One phase 1 study and 2 phase 2 studies have been conducted evaluating relugolix in men with prostate cancer.

Study TB-AK160108 is an ongoing multicenter phase 1, open-label, dose range-finding study conducted in hormone treatment-naïve Asian patients with non-metastatic prostate cancer. The study consists of a dose-rising phase (Part A) and an expansion phase (Part B). In Part A, a loading dose of relugolix (320 or 360 mg) was administered on Day 1 followed by once daily dosing on Days 2 through 28, with the dosage dependent on the individual cohort of 3 to 4

patients each. In Part B, 30 patients receive a maximum of 96 weeks treatment at doses of 80 and 120 mg once daily (N = 15 each arm, loading dose of 320 mg on Day 1). Testosterone reduction by both doses of relugolix was rapid and sustained through 48 weeks. Both the 80- and 120-mg once daily doses were evaluated in phase 2 clinical studies.

Study C27003 is a phase 2 study that enrolled men in North America or the United Kingdom requiring 6 months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily following a single oral loading dose of 320 mg (N = 65) or to degarelix 80 mg subcutaneously every 4 weeks following a single loading dose of 240 mg (N = 38) for 24 weeks. External beam radiation therapy was initiated for most patients between Week 13 and Week 15.

Relugolix 120 mg administered orally once daily rapidly suppressed testosterone levels below the castration threshold (50 ng/dL [1.7 nmol/L]) within the first week of therapy and maintained those levels from the end of Week 4 through at least 24 weeks. The levels of testosterone suppression achieved by relugolix were similar to those achieved by monthly injections of degarelix. Profound castration rates below the lower testosterone threshold of < 20 ng/dL (0.7 nmol/L) were also similar in the relugolix and degarelix groups (Table 2-1).

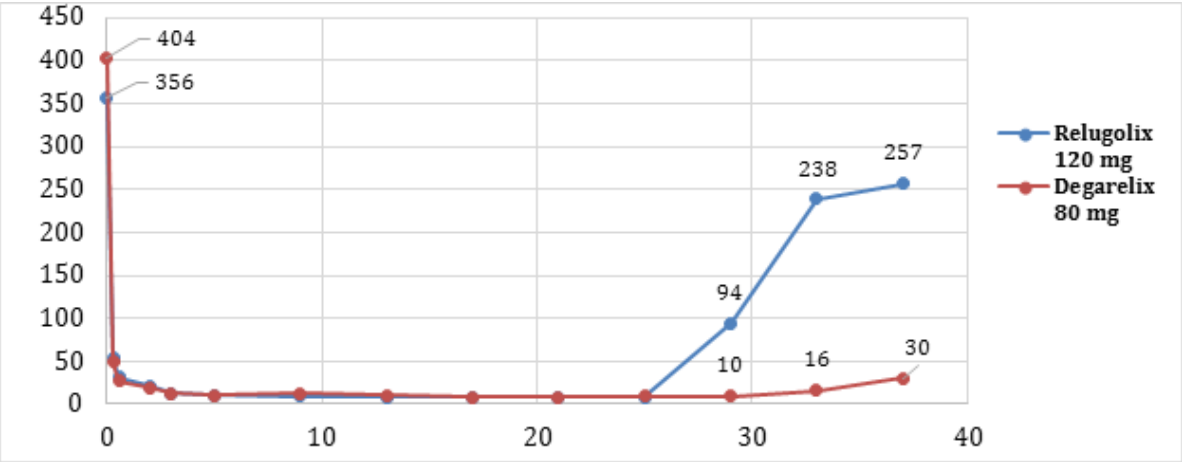
Table 2-1 Study C27003: Sustained Castration Rates (Percentage of Men Achieving Testosterone Suppression to < 50 ng/dL [1.7 nmol/L]) through 24 Weeks

	Relugolix 120 mg QD[a] N = 65	**Degarelix 80 mg Q4W[b] N = 38**
Castration rate over 24 weeks, % (95% CI)	95% (87.1, 99.0)	89% (75.2, 97.1)

Note: Castration rate is defined as the estimated proportion of patients who have testosterone concentrations < 50 ng/dL at all scheduled visits Week 5, Day 1 to specific time point (Week 25, Day 1).
Abbreviations: CI, confidence interval; Q4W, once every 4 weeks; QD, once daily
a. Loading dose of 320 mg on Day 1
b. Loading dose of 240 mg on Day 1, then dosed every month

The percentage PSA reductions and absolute PSA values over time were consistent with the rapid testosterone reductions observed with both therapies and were similar between the relugolix and degarelix treatment arms. Prostate gland size was measured during screening and following 8 to12 weeks of study drug treatment. In both treatment groups, the average reduction in estimated prostate volumes was similar, approximately 30%. Following discontinuation of therapy at the end of 24 weeks, patients were followed for an additional 12 weeks to evaluate testosterone recovery and associated changes in PSA and quality of life. At the end of the follow-up period, approximately half of the patients receiving relugolix had recovered either to the baseline testosterone value or to > 280 ng/dL, whichever was less, compared to only 6% of patients receiving degarelix (Figure 2-1).

Figure 2-1 Study C27003: Testosterone Recovery Following Discontinuation of Relugolix and Degarelix at Week 25



Note: Y-axis shows testosterone value (ng/dL); x-axis shows study week.

Study C27002 is a phase 2 study of relugolix and leuprolide acetate in patients with prostate cancer who require first-line androgen deprivation therapy, which is ongoing in North America. This study was designed to help plan the population, dosing, and assessment schedules for phase 3 studies in patients with advanced prostate cancer. Eligible patients in C27002 have evidence of advanced prostate cancer including either: 1) PSA biochemical relapse following primary surgical or radiation therapy of curative intent; 2) newly diagnosed metastatic prostate cancer; or 3) advanced localized disease for which immediate radiation or surgical therapy is not indicated. In this open-label, parallel group study, patients were randomized to receive 1 of 2 dose levels of oral relugolix (80 or 120 mg [patients randomized to relugolix received a loading dose of 320 mg on Day 1], N = 50 per group) or to an observation cohort to receive standard GnRH therapy with leuprolide acetate 22.5 mg administered by intramuscular injection every 12 weeks (N = 25). Relugolix or leuprolide acetate was administered for up to 48 weeks with patients randomized to leuprolide acetate receiving their last on-study 12-week depot injection at Week 37.

The primary objective of this phase 2 study was to evaluate the ability of relugolix to achieve and maintain testosterone suppression (< 50 ng/dL [1.7 nmol/L]) through Week 25. Results from the completed study C27002 demonstrate that both doses of relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold within the first week of therapy and maintained those levels in 91% of patients through 24 weeks of treatment (Table 2-2).

Table 2-2 Study C27002: Castration Rates (Percentage of Men Achieving Testosterone Suppression to < 50 ng/dL [1.7 nmol/L] through 24 Weeks)

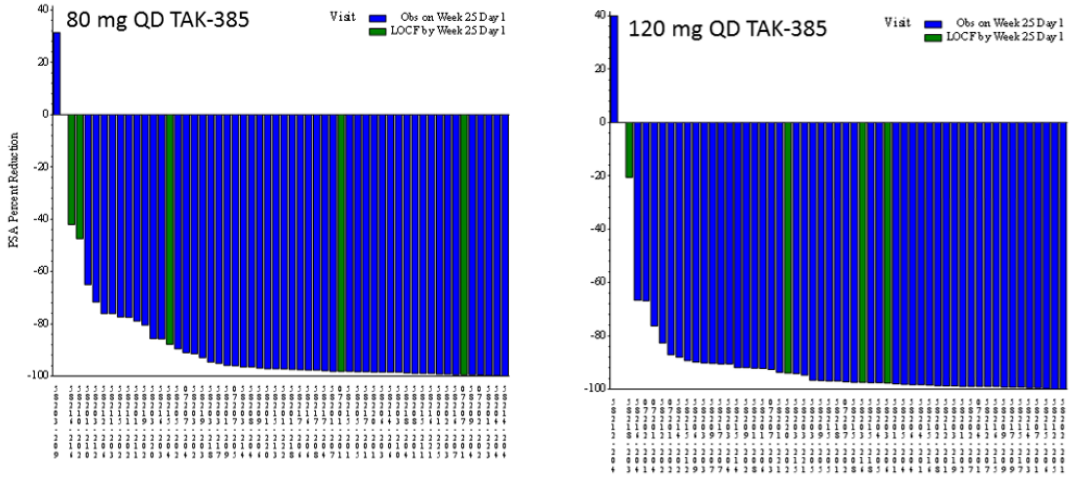
	Relugolix			Leuprolide Acetate 22.5 mg Q12W N = 24
	80 mg QD N = 56	120 mg QD N = 54	Total N = 110	
Patients with at least 1 dose of treatment, n	56	54	110	24
Castration rate[a] over 24 weeks				
n (%)	51 (91)	49 (91)	100 (91)	23 (96)
95% CI[b]	80.4-97.0	79.7-96.9	83.9-95.6	78.9-99.9
Profound castration rate[c] over 24 weeks				
n (%)	39 (70)	41 (76)	80 (73)	18 (75)
95% CI[b]	55.9-81.2	62.4-86.5	63.4-80.8	53.3-90.2

Abbreviations: CI, confidence interval; Q12W, once every 12 weeks; QD, daily

a. Castration rate was defined as the estimated proportion of patients who have testosterone concentrations < 50 ng/dL at all scheduled visits Week 5 Day 1 to specific time point.
b. The 2-sided 95% CI was calculated using the normal approximation method, if the number of non-castration patients was = 5 in any treatment arm, the exact CI was presented.
c. Profound castration rate was defined as the estimated proportion of patients who had testosterone concentrations < 20 ng/dL at all scheduled visits Week 13 Day 1 through specific time point.

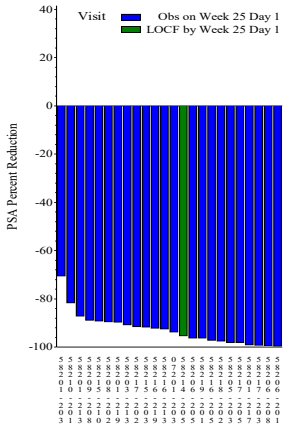
Castration to below the lower testosterone threshold of < 20 ng/dL was also similar in the 2 relugolix arms and to that observed in the leuprolide acetate arm. On average, in patients receiving relugolix, testosterone decreased to below the castration threshold of 50 ng/dL (1.7 nmol/L) by the Day 4 visit, and to below the profound castration threshold of 20 ng/dL (0.7 nmol/L) by the Week 5 visit. In contrast, in patients receiving leuprolide acetate, testosterone levels rose during the first 1 to 2 weeks of therapy and then declined to castrate levels by Week 5. PSA responses between the 2 relugolix arms and leuprolide acetate were similar as demonstrated by PSA waterfall plots showing the reduction in PSA from baseline for individual patients (Figure 2-2 [relugolix] and Figure 2-3 [leuprolide acetate]).

Figure 2-2 Study C27002: Waterfall Plots of Prostate-Specific Antigen Percent Reduction by Dose of Relugolix at Week 25 Day 1



Note: Last observation carried forward method was used to impute percent prostate-specific antigen reductions for patients without an observation at Week 25 Day 1.
Abbreviations: LOCF, last observation carried forward; Obs, observed; PSA, prostate-specific antigen; QD, once daily; TAK-385, relugolix

Figure 2-3 Study C27002: Waterfall Plot of Prostate-Specific Antigen Percent Reduction by Leuprolide Acetate at Week 25 Day 1



Notes:
The leuprolide acetate dose was 22.5 mg every 12 weeks.
Last observation carried forward method was used to impute percent prostate-specific antigen reductions for patients without an observation at Week 25 Day 1.
Abbreviations: LOCF, last observation carried forward; Obs, observed; PSA, prostate-specific antigen

A more detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix

Investigator Brochure, Version 9.0, dated 09 November 2016, along with a full discussion of the safety profile of relugolix.

2.2.4.3. Clinical Safety of Relugolix in Men with Prostate Cancer

A full description of the safety data for relugolix from clinical trials is available in the Investigator Brochure. Overall, approximately 632 healthy volunteers (330 women, 302 men), 535 female patients with uterine fibroids (N = 229) or endometriosis (N = 306), and 218 male patients with prostate cancer received at least 1 dose of relugolix. Data from the 175 patients with prostate cancer who received relugolix in randomized, open-label, parallel-group phase 2 studies, C27002 and C27003, provide the basis for the frequency of expected adverse events associated with relugolix in the prostate cancer indication. The adverse drug reactions in the prostate cancer indication observed in the phase 2 studies include hot flush (59%), fatigue (26%), arthralgia (10%), nausea (5%), and gynecomastia (3%). No clinical evidence of PLD has observed in any relugolix clinical study.

Leuprolide Acetate 3-Month Depot

Leuprolide acetate depot is indicated for the palliative treatment of advanced prostatic cancer.

Leuprolide acetate acts as an agonist at pituitary GnRH (gonadotropin-releasing hormone) receptors. Leuprolide acetate has greater receptor affinity, reduced susceptibility to enzymatic degradation, and is approximately 100-fold more potent than the natural GnRH molecule. GnRH agonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, causing an initial release of both LH and FSH, which causes a subsequent increase in testosterone production from testicular Leydig cells. Initially, leuprolide acetate stimulates LH production, which in turn causes a surge of testosterone and dihydrotestosterone for 5 to 12 days before the ultimate inhibition of LH. This androgen surge of male hormones can cause a flare reaction ("clinical flare"), which may lead to an increase in bone pain, bladder obstruction, or other symptoms due to prostate cancer [Tolis, 1982; Schally, 1980; Waxman, 1985; Conn, 1991; Limonata, 2001].

Chronic stimulation by the GnRH agonist ultimately desensitizes the GnRH receptors, downregulating the secretion of gonadotropins, LH, and FSH, leading to hypogonadism and thus a dramatic reduction in testosterone and dihydrotestosterone, on which continued growth of prostate cancer cells depends. The fall in serum LH leads to a decrease in serum testosterone to castrate levels within 3 to 4 weeks after the start of treatment. Continued treatment maintains serum testosterone at castrate levels.

The decrease in testosterone production is generally reversible over time upon cessation of GnRH agonist therapy. However, testosterone production does not always return to baseline levels and may be related to the duration of GnRH agonist therapy, patient age, and other factors.

The flare phenomenon can be effectively prevented with antiandrogen therapy, which blocks the effect of the increased serum testosterone [Loblaw, 2004]. First generation antiandrogens such as flutamide, bicalutamide, and nilutamide bind to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone. They are often used in an attempt to limit the clinical sequelae produced by the hormonal surge resulting from GnRH agonist treatment.

The most common adverse reactions (> 10%) reported for marketed formulations of leuprolide acetate depot in common use include the following examples:

- Leuprolide (leuprorelin) acetate 11.25 mg: weight fluctuation, hot flash, hyperhidrosis, muscle weakness, bone pain, decreased libido, erectile dysfunction, testicular atrophy, fatigue, injection site reaction [Prostap 3 DCS, 2016]
- Leuprolide acetate 22.5 mg: hot flashes, ecchymoses, erythema, fatigue, injection site burning, injection site paraesthesia [Eligard, 2017]

In post marketing experience, mood swings, depression, rare reports of suicidal ideation and attempt, rare reports of pituitary apoplexy have been reported. Leuprolide has been associated with mild liver enzyme elevations (generally transient and asymptomatic) during therapy in 3-5% of patients; values above 3 times the upper limit of normal are rare, being reported in less than 1% of recipients. A risk of developing or worsening diabetes has been reported in men receiving this class of drug.

The package insert (approved labeling) for the leuprolide acetate study drug provided for this study should be referenced for warnings, precautions, and safety information.

3. STUDY OBJECTIVES AND ENDPOINTS

This phase 3 trial has 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit as listed briefly below and described in detail in the statistical analysis plan. Patients enrolled into this phase 3 trial will be randomized 2:1 to either relugolix 120 mg once daily following an oral loading dose of 360 mg on Day 1, or to leuprolide acetate 22.5 mg (or 11.25 mg Japan, Taiwan, and China) 3-M depot injection. Patients randomized to leuprolide acetate will also receive an antiandrogen if indicated at the discretion of the investigator.

The first criterion for the primary efficacy endpoint will evaluate only patients randomized to relugolix. The second criterion for the primary efficacy endpoint will evaluate the non-inferiority of patients randomized to relugolix to those randomized to leuprolide acetate as described below.

Objectives	Endpoints
Primary	
• To evaluate the ability of relugolix to achieve and maintain serum testosterone suppressed to castrate levels of ≤ 50 ng/dL (1.7 nmol/L) in patients with androgen-sensitive advanced prostate cancer.	The primary endpoint is the sustained castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). • Evaluation Criterion 1: to determine whether the sustained castration rate (defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL [1.7 nmol/L] while on study treatment from Week 5 Day 1 through Week 49 Day 7) for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be at least 90% to meet this criterion. • Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot injection as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.
Secondary	
• To evaluate the time course and change in serum testosterone during treatment with relugolix;	• Describe effects on serum testosterone: o Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4 and prior to dosing on Week 3 Day 1; o Profound castration rate defined as the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) while on treatment from Week 25 Day 1 through Week 49 Day 1);

Objectives	Endpoints
• To evaluate the time course and magnitude of PSA reduction during treatment with relugolix;	• Describe effects on PSA: o Proportion of patients with confirmed PSA response (by Prostate Cancer Clinical Trials Working Group 3 [Scher, 2016]) at the Week 3 and Week 5 visits; o Proportion of patients with PSA concentration < 0.2 ng/mL [0.2 µg/L] at the Week 25 visit;
• To evaluate testosterone recovery following discontinuation of relugolix;	• Time to testosterone recovery in approximately 100 patients randomized to relugolix and approximately 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of leuprolide acetate 3-M depot);
• To evaluate quality of life using validated patient-reported outcome instruments;	• Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable during the Follow-up and/or End of Treatment visits; • Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as the EuroQol EQ-5D-5L questionnaire, at regular intervals during treatment, and as applicable during the Follow-up visits;
• To evaluate the safety of relugolix 120 mg once daily in men with androgen-sensitive advanced prostate cancer;	• Incidence of adverse events; • Incidence of abnormalities in clinical laboratory data;
• To evaluate the effect of relugolix and leuprolide acetate on endocrine pharmacodynamic parameters;	• Endocrine marker effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for: o LH at the Day 4, Week 5, Week 25, and Week 49 visits; o FSH at the Day 4, Week 5, Week 25, and Week 49 visits; o Dihydrotestosterone at the Week 5, Week 25, and Week 49 visits; o Sex hormone binding globulin at the Week 5, Week 25, and Week 49 visits;

Objectives	Endpoints
• To collect relugolix plasma concentration data to further evaluate relugolix population PK and the relationship between relugolix exposure and serum testosterone; and	• Predose relugolix plasma concentrations;
• To characterize the relugolix plasma PK parameters in a subset of patients from China (if enrolled) and Japan;	• Single and repeat-dose plasma relugolix PK parameters such as C_{max}, $AUC_{0-\tau}$, and t_{max}.
• To describe the time course and magnitude of PSA progression and development of castration resistant prostate cancer during treatment with relugolix;	• Time to PSA progression • Proportion of patients with confirmed PSA progression among those who have achieved sustained testosterone suppression during the 48-week treatment
Exploratory	
• To explore the overall survival of patients treated with relugolix; and	• Overall survival defined as time from randomization to date of death prior to data cutoff date;
• To explore the contribution of genetic variance on drug response.	• The presence of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The HERO study is a phase 3 multinational randomized, open-label, parallel-group study to evaluate the safety and efficacy of relugolix in patients with androgen-sensitive advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy. Relugolix is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist that lowers testosterone by inhibiting pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Relugolix 120 mg orally once daily or leuprolide acetate depot suspension 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) every 3-months (3-M) will be administered to patients with prostate cancer who require androgen deprivation therapy. This study will evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) for 48 weeks in patients with androgen-sensitive advanced prostate cancer.

To be eligible for the study, a patient must be, in the opinion of the investigator, a candidate for at least 1 year of continuous androgen deprivation therapy for the management of androgen-

sensitive advanced prostate cancer and must not be a candidate for surgical therapy. Eligible patients include those with evidence of biochemical relapse (rising PSA) following local primary intervention with curative intent, newly diagnosed metastatic disease (excluding metastases to the brain), and/or advanced localized disease. Patients may receive radiotherapy, cryotherapy or high frequency ultrasound no sooner than 2 months after initiation of androgen deprivation therapy. Patients may be included if they have not previously received androgen deprivation therapy for more than 18 months, and if the androgen deprivation therapy was completed at least 3 months prior to baseline. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy. Baseline serum testosterone must be ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L) to be enrolled.

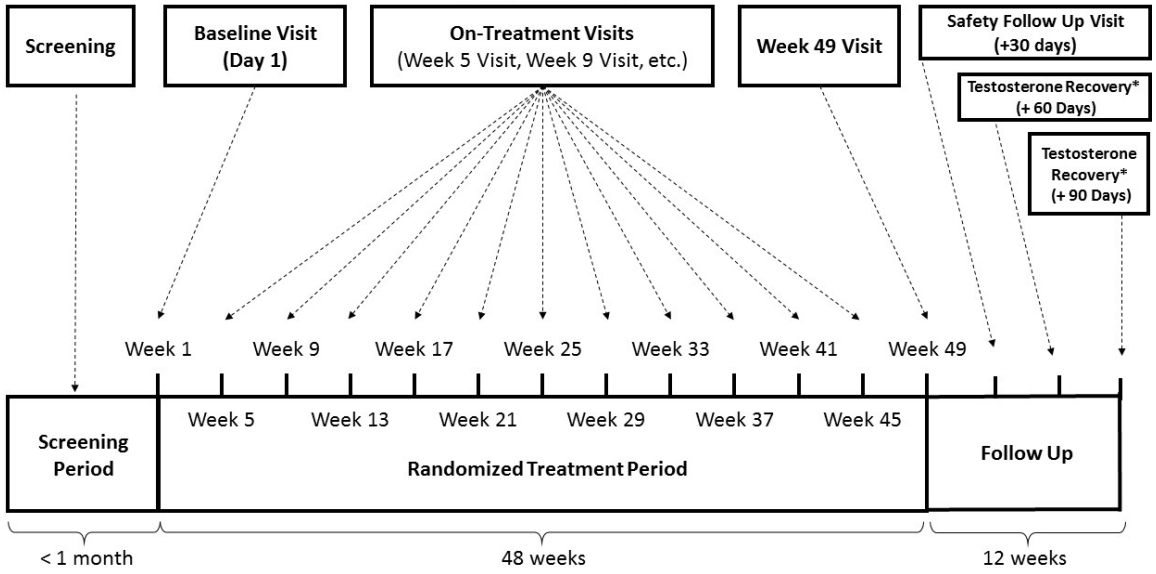
Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg once daily following a loading dose of 360 mg on Day 1 or 3-M depot of leuprolide acetate 22.5 mg (or 11.25 mg in Japan, Taiwan, and China). After randomization, patients on the leuprolide acetate arm may receive an antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator. Randomization will be stratified by geographic region, presence of metastatic disease, and age.

Approximately 915 patients will be enrolled in this study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region. The study includes a Screening Period of up to 28 days, a Treatment Period of 48 weeks, and a Follow-up Period of up to 90 days. Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed. Eligible patients will receive study treatment for 48 weeks. During that time, testosterone and PSA will be assessed monthly and patient-reported outcomes (EORTC-QLQ-C30, EORTC-QLQ-PR25, EuroQol EQ-5D-5L) will be assessed approximately every 3 months during the Treatment Period and more frequently during the Follow-up Period. Additional serum endocrine evaluations will include: LH, FSH, dihydrotestosterone, and sex hormone binding globulin. Relugolix PK samples will be collected throughout the study. Full PK profiles will be determined in a subset of patients in China (if enrolled) and Japan. Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead ECG, and visual acuity tests.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (testosterone level ≤ 50 ng/dL [1.7 nmol/L]), should remain on study and may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide. For patients requiring other systemic antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.

A schematic of the overall study design is provided in Figure 4-1.

Figure 4-1 Schematic of Study Design



Relugolix dosed daily (Baseline Day 1 – Week 48 Day 7)
Leuprolide Acetate dosed every 12 weeks (Baseline Day 1, Week 13 Day 1, Week 25 Day 1, and Week 37 Day 1)
*+60 Days and +90 Days Testosterone Recovery visits in subset of patients

4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is designed to establish the safety and efficacy of relugolix 120 mg orally once daily in men with advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy for androgen-sensitive disease. This study will focus on the primary objective of evaluating the ability of relugolix to achieve and maintain suppression of serum testosterone to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) in patients with advanced prostate cancer. During the Treatment Period of the study (Day 1 to Week 49 [Study Day 337]), patients will be randomized to one of the study treatment arms: oral loading dose of relugolix (360 mg) followed by 120 mg once daily of relugolix or leuprolide acetate 3-M depot injection of 22.5 mg (or 11.25 mg Japan, Taiwan, and China) at 12-week intervals for 48 weeks. Patients treated with leuprolide acetate will also receive an antiandrogen for 4 weeks or longer if indicated in the opinion of the investigator.

The study is designed to allow for global approvals, however, different regulatory agencies require different criteria for the demonstration of efficacy. The United States (US) Food and Drug Administration (FDA) requires, for approval, a primary efficacy criterion to determine whether the sustained castration rate (defined as the cumulative probability of testosterone ≤ 50 ng/dL [1.7 nmol/L] while on relugolix study treatment from Week 5 Day 1 through Week 49 Day 1) is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion. The study includes a leuprolide acetate arm to meet the regulatory requirement of other regions to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot injection as

assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.

The dose of relugolix selected is based on data from phase 1 and 2 studies demonstrating that oral doses of 80 mg and 120 mg once daily following an oral loading dose of 320 mg were able to suppress testosterone to castrate levels (see Section 2.2.4.2 and the Investigator Brochure). A loading dose of 360 mg (three 120-mg tablets) was selected for phase 3 so that only one tablet size was required. Leuprolide acetate 3-M depot injection was selected as the comparator as this is the GnRH agonist used most commonly as standard of care in the population under evaluation. Degarelix, an injectable GnRH antagonist, was considered, but was not used as it has limited market uptake attributed at least in part to a significant number of injection site reactions.

4.3. Selection of Study Population

Approximately 915 men with advanced prostate cancer requiring androgen deprivation therapy will be enrolled in this study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region. Enrollment is defined as the time at which a patient is randomized to a treatment group and receives at least one dose of study drug.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor prior to randomizing the patient.

4.3.1. Inclusion Criteria

A patient will be eligible for inclusion in this study only if all of the following inclusion criteria are met prior to randomization, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a male aged 18 years or older on the day of signing and dating the informed consent form;
3. Has histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate;
4. Is a candidate for, in the opinion of the investigator, at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer with one of the following clinical disease state presentations:
    a. Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, such as surgery, radiation therapy, cryotherapy, or high-frequency ultrasound and not a candidate for salvage treatment by surgery; or
    b. Newly diagnosed androgen-sensitive metastatic disease; or
    c. Advanced localized disease unlikely to be cured by local primary intervention with either surgery or radiation with curative intent;

Note: radiotherapy, cryotherapy, or high frequency ultrasound are allowed after 2 months of androgen deprivation therapy.

5. Has a serum testosterone at the Screening visit of ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L);
6. Has a serum PSA concentration at the Screening visit of > 2.0 ng/mL (2.0 µg/L), or, when applicable, post radical prostatectomy of > 0.2 ng/mL (0.2 µg/L) or post radiotherapy, cryotherapy, or high frequency ultrasound > 2.0 ng/mL (2.0 µg/L) above the post interventional nadir;
7. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at initial screening and at baseline (refer to Appendix 1);
8. Is a male patient who, even if surgically sterilized (ie, status post vasectomy):
    a. Agrees to use a male condom if having sex with a woman of childbearing potential or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or
    b. Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception;
9. Must agree not to donate sperm from first dose of study drug through 4 months after the last dose of study drug;
10. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

4.3.2. Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

1. In the investigator's opinion, is likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating androgen deprivation therapy;
2. Previously received GnRH analog or other form of androgen deprivation therapy (estrogen or antiandrogen) for > 18 months total duration. If androgen deprivation therapy was received for ≤ 18 months total duration, then that therapy must have been completed at least 3 months prior to baseline. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot;
3. Previous systemic cytotoxic treatment for prostate cancer (e.g. taxane-based regimen);
4. Metastases to brain per prior clinical evaluation;
5. *Removed*;
6. Scheduled for major surgery after baseline;
7. History of surgical castration;

8. Active malignancy beyond prostate cancer ***with the exception*** of any of the following:
   - Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ carcinoma of any type
   - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for ≥ 2 years
   - Any other cancer from which the subject has been disease-free for ≥ 5 years

   The medical monitor should be contacted for any questions regarding this exclusion criterion.
9. Abnormal laboratory values at the Screening visit that suggest a clinically unstable underlying disease, or the following laboratory values:
   a. Serum gamma-glutamyl transferase > 2.0 x ULN;
   b. Serum ALT and/or AST > ULN;
   c. Total bilirubin > ULN (unless secondary to Gilbert's syndrome or the pattern is consistent with a diagnosis of Gilbert's syndrome) or;
   d. Serum creatinine > 2.0 mg/dL (176.8 µmol/L);
   e. Platelets < 100 x 10^3/µL or history of bleeding disorder;
   f. Hemoglobin < 10.0 g/dL (100 g/L);
   g. Leukocytes (WBC) < 3 x 10^3/µL (3 GI/L);
   h. Absolute neutrophil count < 1.5 x 10^3/µL (1.5 GI/L);
10. Hemoglobin A1c (HbA1c) > 10% in patients previously diagnosed with diabetes mellitus. HbA1c > 8% in patients whose diabetes mellitus is previously undiagnosed. (Excluded patients may be rescreened after referral and evidence of improved control of their condition);
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (hepatitis A virus IgM positive), hepatitis B (HBsAg positive), or hepatitis C (HCV antibody positive, confirmed by HCV ribonucleic acid);
12. Known human immunodeficiency virus infection;
13. Any of the following within 6 months before Baseline Day 1:
    a. Myocardial infarction;
    b. Unstable angina;
    c. Unstable symptomatic ischemic heart disease;
    d. New York Heart Association (NYHA) class III or IV heart failure
    e. Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events);
    f. Any other significant cardiac condition (e.g., pericardial effusion, restrictive cardiomyopathy, severe untreated valvular stenosis, or severe congenital heart disease);
14. The following ECG abnormalities are excluded:

a. ECG evidence of acute ischemia;

b. Q-wave infarction, unless identified 6 or more months before the Screening visit;

c. QTc > 470 msec, measured by Fridericia's formula [QTcF = QT/(RR^0.33)]. If the QTc is prolonged in a patient with a pacemaker, the patient may be enrolled in the study if confirmed by the medical monitor;

d. Congenital long QT syndrome;

e. Active conduction system abnormalities. Examples of active conduction system abnormalities include the following:

- Mobitz II second degree heart block without a permanent pacemaker in place;
- Third degree heart block without permanent pacemaker in place;
- Untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
- Clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes;
- Uncontrolled atrial fibrillation (patients with chronic stable atrial fibrillation on stable anticoagulant therapy or patients with stable cardiac rhythm controlled by a pacemaker are allowed);

15. *The following exceptions are allowed:* First degree atrioventricular (AV) block, second degree AV block Type 1 (Mobitz Type 1/Wenckebach type), or right bundle branch block.Uncontrolled hypertension despite appropriate medical therapy (sitting blood pressure of greater than 160 mmHg systolic and/or 100 mmHg diastolic at 2 separate measurements no more than 45 minutes apart during the Screening visit). Patients may be re-screened after referral and further management of hypertension;
16. Hypotension, as indicated by systolic blood pressure < 84 mmHg on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming upright position;
17. Bradycardia as indicated by a heart rate of < 45 beats per minute on the ECG at the Screening or Baseline Day 1 visit;
18. Treatment with any investigational product within 28 days or 5 half-lives (whichever is longer);

    Exception: treatment for prostate cancer with any investigational products where the mechanism of action is testosterone lowering. In this circumstance, there must be a minimum 12-month treatment free interval.
19. *Removed*;
20. Previous treatment with relugolix in a clinical study;
21. Patient is a study site employee or is a primary family member (spouse, parent, child, or sibling) of a site employee involved in the conduct of the study;

22. Known gastrointestinal disease or procedure that could interfere with the oral absorption or tolerance of relugolix, including inability to swallow whole tablets or conditions that may interfere with absorption at the level of the small intestine. Examples of such conditions include but are not limited to Crohn's disease, gastric bypass, active peptic ulcer disease, and gastrectomy. The medical monitor should be contacted for any questions regarding this exclusion criterion;
23. Use or planned use of any medication listed in the prohibited medications table (see Section 5.10.1) without the appropriate washout period;
24. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
25. Has a prior (within 1 year of the Screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
26. Any other medical or psychiatric condition that, in the opinion of the investigator, would interfere with completion of treatment according to this protocol.
27. Weight ≥ 400 pounds (181 kg) or has a body mass index ≥ 50;

4.4. Other Eligibility Criteria Considerations

Patient eligibility may require additional or repeat assessments such as safety labs, vital signs, or ECG during the Screening Period.

To assess any potential impact on patient eligibility with regard to safety, the investigator is referred to the Investigator Brochure for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) used in this study.

4.5. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the Screening Period. Study site personnel will access the interactive voice/web recognition system (IWRS) to assign a screening identification number to a potential patient.

For patients who provide informed consent and subsequently do not meet eligibility criteria, or withdraw consent are considered screen failures and are not randomized. Study site personnel should ensure that the source record includes documentation for the screen failure (eg, medical history, eligibility criteria, procedures performed).

Patient numbers assigned to patients who become screen failures are not to be reused. Patient identification numbers will be assigned to eligible patients at randomization, as described in Section 4.6.

4.6. Method of Assigning Patients to Treatment Group and Patient Identification Number

After a patient is screened and the investigator determines that the patient is eligible for enrollment, the site staff will complete the Randomization Authorization Form and send it to the sponsor (Myovant Sciences GmbH) or sponsor designee per the instructions in the investigator site file. The sponsor (or designee) will approve the patient's enrollment in writing. Once the site has received approval, the patient may undergo the Baseline Day 1 visit. The site will randomize the patient to treatment by using the IWRS during the patient's Baseline Day 1 visit. The IWRS will assign the patient identification (ID) number. This number will identify the patient for the duration of the study. A study treatment kit number will be available at the site according to the randomization code.

4.7. Removal of Patients from Therapy

Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Week 49 visit on the Schedule of Activities. The End of Treatment is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.

Follow-up visits to assess safety will be performed in all study patients. If the patient plans to start alternative androgen deprivation therapy less than 30 days after the End of Treatment visit, the Safety Follow-up visit may occur earlier, before the start of the alternative androgen deprivation therapy. Testosterone recovery will be evaluated in approximately 100 patients randomized to relugolix and approximately 50 patients to leuprolide acetate who complete 48 weeks of study drug treatment and, in the opinion of the investigator, are candidates for intermittent androgen deprivation therapy and will not be offered alternative androgen deprivation therapy upon completion of study therapy. These patients will return for the 60- and 90-day follow-up Testosterone Recovery visits.

The safety and/or compliance events shown in Table 4-1 will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved.

Table 4-1 Removal of Patients from Treatment

Reason	Comment
Adverse event or intercurrent illness	Any intolerable adverse event to the patient that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued
Failed to meet eligibility criteria post randomization	If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health
Dose hold	Relugolix dose hold that exceeds 10 consecutive days

Reason	Comment
Patient not meeting criteria for testosterone suppression to castrate level	Patients with disease progression while on study drug, assuming adequate testosterone suppression (testosterone level ≤ 50 ng/dL [1.7 nmol/L]), may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide. For patients requiring other systemic antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.
Laboratory abnormality defined by protocol: ALT or AST > 8 x ULN; or ALT or AST > 5 x ULN and persists for more than 2 weeks; or ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or INR > 1.5; or ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)	If any of these liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status).
Confirmed QTc prolongation of more than 500 msec, in the absence of a pacemaker, as read by a cardiologist	If QTc prolongation of > 500 msec in the absence of a pacemaker occurs, the ECG must be repeated. Confirmed QTc prolongation, measured by Fridericia's formula [QTcF = QT/(RR^0.33)], will result in removal of the patient from treatment.
Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist that may be related to study drug treatment	
Gross noncompliance with protocol	Patients who are, in the opinion of the investigator or the medical monitor, non-compliant with the protocol's requirements
Patient decision	Patients may permanently discontinue study treatment at any time for any reason. Following study drug discontinuation, patients should attend the protocol-required safety follow-up visit.
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime as described in Section 10.3.3. The sponsor will terminate this study following completion of study objectives, or earlier if deemed necessary.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; INR, international normalized ratio; QTc, QT interval corrected for heart rate; QTcF, QT interval corrected for heart rate using the Fridericia formula; ULN, upper limit of normal

Once study drug has been discontinued, all study procedures outlined for the Week 49 visit will be completed as specified in the Schedule of Activities (Section 1.1). The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who withdraw from treatment will not be replaced.

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. Patients randomized to relugolix should be counseled to notify the investigator in the event of intercurrent illness to determine if the study drug treatment can be continued. Every effort should be made to ensure the patient's compliance with study drug treatment, including calling patients to reschedule missed visits.

In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should attempt at least 3 documented telephone calls and, if necessary, a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.8. Contraception/Pregnancy Avoidance

It is not known what effects relugolix has on human pregnancy or development of the embryo or fetus. Therefore, male patients should avoid impregnating a female partner.

A patient must use a condom if having sex with a pregnant woman. Patients must not donate sperm from first dose of study drug through 4 months after the last dose of study drug.

Nonsterilized male patients should use a male condom, either alone or in addition to effective methods of contraception used by a female partner of childbearing potential, through defined periods during and after study treatment as specified below. Examples of effective contraceptive methods include condoms, hormonal contraceptives, and intrauterine devices.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to one of the following:

- Use a male condom if having sex with a woman of childbearing age or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods for the female partner, and withdrawal are not acceptable methods of contraception.

5. TREATMENTS

5.1. Treatments Administered

Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg following a loading dose of 360 mg on Day 1, or leuprolide acetate 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) 3-M depot injection (plus antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator). Randomization will be stratified by geographic region, presence of metastatic disease, and age**.**

Approximately 915 patients will be enrolled in the study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region.

Study treatment is defined as either oral relugolix or leuprolide acetate injection (see Table 5-1).

Table 5-1 Description of MVT-601-3201 Study Drugs

	Study Treatment	
Product name:	Relugolix	Leuprolide Acetate 3-M Depot
Formulation description:	Round film coated pink tablet	
Dosage form:	Tablet	
Unit dose strength and dosage level:	120 mg, following a single-loading dose of 360 mg	22.5 mg (11.25 mg in Japan, Taiwan, and China)
Route of Administration / Duration	Oral / 48 weeks[a]	Subcutaneous or intramuscular / 48 weeks[a]

a. Duration of treatment is 48 weeks during the Treatment Period; the last leuprolide acetate injection occurs 12 weeks before the end of the Treatment Period.

5.2. Identity of Investigational Product

Relugolix has the chemical name N-(4-(1-(2,6-difluorobenzyl)-5-((dimethylamino)methyl)-3-(6-methoxy-3-pyridazinyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-6-yl)phenyl)-N'-methoxyurea.

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using the US Pharmacopeia and the National Formulary excipients.

5.3. Randomization and Stratification

Patients are assigned to one of 2 treatment arms in accordance with the randomization schedule using an integrated randomization system (IWRS).

At Baseline Day 1, patients will be randomized in a 2:1 ratio to one of the following treatment arms:

Treatment Arm	Randomized Treatment	Approximate Number of Patients
Arm A	Relugolix 360 mg (three 120 mg tablets) single oral loading dose on Day 1 followed by 120 mg orally once daily	610
Arm B	Leuprolide acetate, 22.5 mg 3-M depot[a] injection (or 11.25 mg in Japan, Taiwan, and China)	305

a. Antiandrogen is administered for the first 4 weeks or longer if indicated, in the opinion of the investigator.

Randomization will be stratified by geographic region, presence of metastatic disease, and age age as follows:

- Geographic Region
  - Europe;
  - North and South America; or
  - Asia and Rest of World.
- Presence of Metastatic Disease
  - Metastatic disease diagnosed on locally-read imaging by abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) or bone scan at the time of the Baseline Day 1 visit; or
  - No evidence of metastatic disease by locally-read imaging.
- Baseline Age
  - ≤ 75 years old; or
  - > 75 years old.

5.4. Directions for Administration

Relugolix

Relugolix 120-mg tablet strength will be available as immediate-release film-coated tablets. These tablets will be presented in 45-tablet bottle packaging and dispensed to patients every 4 weeks at scheduled study visits.

All protocol-specific criteria for administration of study drug must be met and documented prior to study drug administration. Study drug will be dispensed by study personnel only to eligible patients who are under the supervision of the investigator or identified subinvestigator(s). If a blood draw or any study procedure coincides with a meal, the study procedure will take precedence, followed by the blood draw, and then the meal.

At the Baseline Day 1 visit, the site will administer a single loading dose of oral relugolix 360 mg (3 tablets).

Patients randomized to relugolix will be instructed to take one tablet on an empty stomach at least 1 hour before breakfast once daily. If the dose is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

Patients may consume water ad libitum. Patients should swallow the study medication whole and not chew it or manipulate it in any way before swallowing.

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK and pharmacodynamic samples are collected.

Leuprolide Acetate

Leuprolide acetate 3-M depot injection, 22.5 mg (or 11.25 in Japan, Taiwan, and China), will be administered every 12 weeks. Leuprolide acetate 3-M depot will be administered on Day 1 at the clinic, then at 12-week intervals (see Schedule of Activities, Section 1.1) and investigators should follow product instructions provided by the manufacturer. An antiandrogen may be administered for the first 4 weeks or longer if indicated, as determined by the investigator, and/or as indicated by disease status (eg, in patients with extensive localized symptomatic disease or with metastatic disease).

Possible antiandrogen options include, but are not limited to, bicalutamide, flutamide, and nilutamide.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that is related to study drug and cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted if the investigator believes it is in the best interest of the patient to interrupt relugolix dosing until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 10 consecutive days for evaluation and treatment of an adverse event. Patients may subsequently be re-started on study drug, with the written approval of the sponsor (or designee).

5.6. Dose Escalation, Dose Reduction, and Dose Interruption

Neither dose escalations nor dose reductions are allowed in the study.

Every effort should be made to continue relugolix administration through treatment-emergent adverse events unless they are grade 3 or 4 and related to study drug, or the investigator believes it is in the best interest of the patient to interrupt relugolix dosing. Of note, patients on leuprolide acetate 3-M depot injection continue to receive GnRH agonist therapy because it is impossible to discontinue treatment.

If the grade 3 or 4 adverse event improves to grade 0, 1, or 2 after holding the dose, or if the adverse event is no longer believed to be related to study drug, the patient may be rechallenged at the same dose at the discretion of the investigator and medical monitor. If the adverse event remains grade 3 or grade 4 after treatment discontinuation and the investigator continues to believe the adverse event is related to study drug, study drug treatment should be discontinued permanently.

5.7. Storage, Packaging, and Labeling

Relugolix will be packaged in bottles containing 45 120-mg tablets of relugolix. Additional details regarding the packaging of relugolix are provided in the Investigator Brochure and investigator site file.

Leuprolide acetate 11.25 mg or 22.5 mg 3-M depot injection will be packaged and labeled for clinical trial use.

Relugolix medication should be stored in an appropriate, limited-access, secure location, protected from light, in the original bottles and within a temperature range at 15°C to 25°C (59°F to 77°F) with excursions permitted up to 30°C (86°F).

A daily temperature log of the drug storage area must be maintained every working day.

Study drug must be stored under the conditions specifie, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Patients will be instructed to store study drug at room temperature out of the reach of children.

Further guidance and information for final disposition of unused study drug are provided in the investigator site file. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Refer to the leuprolide acetate product labeling for information regarding the proper storage and handling of leuprolide acetate.

5.8. Blinding

Blinding is not applicable; this is a randomized open-label study.

5.9. Study Drug Accountability and Treatment Compliance

Patients should bring all unused study drug to each study visit. Study drug accountability will be conducted and results will be recorded as the primary source of study drug accountability. If a patient is persistently noncompliant with the study treatment, it may be appropriate to withdraw the patient from the study.

All patients should be reinstructed regarding dosing compliance during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance.

Patients randomized to relugolix should be counseled to notify the investigator in the event of intercurrent illness to determine if the study drug treatment can be continued. Should a patient need a surgery of any kind, please contact the medical monitor. Every effort should be made to ensure the patient's compliance with study drug treatment, including calling patients to reschedule missed visits.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-2 provides examples of systemic medications that are prohibited prior to the first dose of study medication until the End of Treatment visit and the Follow-up Period is complete. This list is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class. Patients may "wash out" of these prohibited medications prior to dosing based on the periods provided in Table 5-2.

Any investigational agent for the treatment of prostate cancer where the mechanism of action is testosterone lowering, including agents that are commercially available for indications other than prostate cancer that are under investigation for the treatment of prostate cancer, are also prohibited for at least 12 months prior to the first dose of study medication.

Table 5-2 Prohibited Medications and Washout Periods

Drug Class	Examples		Minimum Washout Period[c]
GnRH analogues	Leuprolide acetate injection[a] Goserelin acetate injection		At least one dosing interval of the depot preparation; minimum of 3 months[d]
GnRH antagonists	Degarelix		At least one dosing interval of the depot preparation; minimum of 3 months[d]
Antiandrogens[a]	Bicalutamide Flutamide	Nilutamide Enzalutamide[b]	3 months
CYP17 inhibitors	Abiraterone acetate + prednisone		3 months
Other androgen suppressing agents or androgens	Estrogens Ketoconazole Testosterones	Megestrol acetate Progestogens	3 months
5-alpha reductase inhibitors	Finasteride Dutasteride		4 weeks 6 months
Class IA an III antiarrhythmics	Amiodarone Procainamide	Quinidine Sotalol	2 weeks (3 months for amiodarone)

Drug Class	Examples		Minimum Washout Period[c]
Moderate and strong CYP3A and P-glycoprotein inducers	Bosentan Carbamazepine Efavirenz Etravirine Mitotane Modafinil Nafcillin	Phenobarbital Phenytoin Rifampin St John's Wort Primidone Rifabutin Rifapentine	1 week Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.
Moderate/strong P-glycoprotein inhibitors	Amiodarone Azithromycin Captopril Carvedilol Clarithromycin Conivaptan Cyclosporin Diltiazem Dronedarone Eliglustat Erythromycin	Felodipine Itraconazole Ketoconazole Lapatinib Lopinavir/Ritonavir Quercetin Quinidine Ranolazine Ticagrelor Verapamil	1 week (3 months for amiodarone) (3 months for ketoconazole) Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.
Herbal therapies	Chinese herbs Ginkgo biloba	Kava kava Ginseng	2 weeks or 5 half-lives (whichever is shorter)

Abbreviation: CYP, cytochrome P450

a. Unless randomized to leuprolide acetate control arm of this study. After randomization, antiandrogen therapy is permitted for the first 4 weeks or longer of leuprolide acetate treatment.
b. Enzalutamide is allowed for the treatment of castration-resistant disease that occurs on study (rising prostate-specific antigen in the setting of testosterone suppressed to castrate levels (≤ 50 ng/dL [1.7 nmol/L]).
c. Minimum washout period is calculated from the date of last dose of prohibited medication to the first day of study drug.
d. Patients with cumulative previous androgen deprivation therapy > 18 months are excluded, regardless of washout period.

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded. At a minimum, the drug generic name, dose amount, route of administration, start date, and stop date will be recorded in the source documents and the eCRF.

If alternative androgen deprivation therapy is initiated prior to 30 days after the last relugolix dose, record the alternative androgen deprivation therapy as a concomitant medication.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]), should be encouraged to remain on study and, if indicated, may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide. For patients requiring other systemic

antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.6. Further details of the procedures are provided in the investigator site file.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Section 1.1). The study is divided into 3 periods: Screening Period, Treatment Period, and Follow-up Period. Unscheduled visits may also occur as needed to evaluate patients.

6.2. Screening Period (Day -28 to Day -1)

The Screening Period will be from Day -28 through Day -1. At the Screening visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent before any study-specific procedures are conducted, unless the procedures are part of routine standard of care. The informed consent process must be documented in the patient's clinical record.

The investigator will assess and confirm the eligibility of each patient and determine that each patient will maintain study drug compliance during the treatment period. All screening procedures results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

The following assessments will be performed:

- Complete medical history, including detailed prostate cancer history;
- Vital signs, weight, and height;
- 12-lead ECG;
- ECOG performance assessment;
- Complete physical exam and visual acuity assessment;
- An abdominopelvic CT or MRI and a bone scan should be performed and read locally to determine the presence of metastatic disease within 60 days prior to randomization. However, if CT or MRI demonstrates presence of metastatic disease, a bone scan is not required. If metastatic disease is not present on CT or MRI, then a bone scan is also required.
- Demographics;
- Laboratory data collection (see Section 1.1);
- Verify inclusion/exclusion criteria; and
- Concomitant medications and adverse events.

A Randomization Authorization Form must be submitted to the sponsor for approval prior to conducting the Baseline Day 1 visit.

6.3. Treatment Period (Day 1 to Week 49 [Study Day 337])

Baseline Day 1 Visit

Study site personnel should ensure that an approved Randomization Authorization Form is in the patient's file before proceeding with the randomization and Day 1 visit procedures. Patients will be randomized to either relugolix or leuprolide acetate 3-M depot injection 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) (see Section 5.3).

The following assessments will be performed:

- Patient-reported outcome questionnaires (EQ-5D-5L, EORTC-QLQ-PR25, and EORTC-QLQ-C30)
  - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Medical history;
- Vital signs and weight;
- 12-lead ECG;
- ECOG performance assessment;
- Symptom-based physical examination;
- Verify inclusion/exclusion criteria;
- Concomitant medications and adverse events;
- Randomize the patient;
- Laboratory collection (see Section 1.1); and
- Study drug management:
  - If study drug administration is not logistically feasible on the same day as randomization, Day 1 will be defined as the day of the first dose.
  - If the patient is randomized to relugolix, site personnel will administer a single loading dose of oral relugolix 360 mg (3 tablets) and then dispense study drug to the patient and instruct on daily dosing of 120 mg (1 tablet) and the importance of medication compliance (see Section 5.4);
  - If the patient is randomized to leuprolide acetate, site personnel will administer the injection in the clinic.

Day 4 and Weeks 2 and 3 Visits (Visit Window ± 2 days)

The following assessments will be performed:

- Vitals signs;
- Laboratory collection (see Section 1.1); and
- Concomitant medications and adverse events.

Note: The Week 2 visit will only occur for patients who are part of the Japan or China subset for PK analysis.

Weeks 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, and 45 Visits (Visit Window ± 7 Days)

Importantly, patients randomized to relugolix should be called 7 days before each visit to ensure the patient is compliant with study drug medication.

The following assessments will be performed:

- Patient-reported questionnaires will be completed on the electronic tablet provided (Weeks 5, 13, 25, and 37 only)
    - Patients will complete the questionnaires before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs, weight
    - Weight will be collected only on Weeks 13 and 25;
- 12-lead ECG (Weeks 5, 13, and 25 only);
- ECOG performance assessment (Week 25 only);
- Symptom-based physical examination (except Week 25);
- Complete physical exam and visual acuity assessment (Week 25 only);
- Laboratory collection (see Section 1.1)
    - Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose, approximately 24 hours after the previous dose. Patients may be dosed in the clinic at these visits, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing.
- Concomitant medications and adverse events; and
- Study drug management:
    - For patients randomized to relugolix,
        - Perform study drug accountability;
        - Dispense study drug. Patients may be dosed in the clinic, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing;
        - Remind patients on importance of medication compliance.
    - For patients randomized to leuprolide acetate,
        - Site will administer leuprolide acetate in clinic every 12 weeks (Weeks 13, 25, and 37).

Week 49 or (Early Termination of Study Drug) (Visit Window ± 7 Days)

- For patients receiving relugolix, a member of the site team will call the patient 7 days before the Week 49 visit to remind the patient of the need for compliance with their study medication;
- Patient-reported outcome questionnaires
    - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs, weight;
- 12-lead ECG;
- ECOG performance assessment;
- Complete physical exam and visual acuity assessment;

- Laboratory collection (see Section 1.1);
    - Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose, approximately 24 hours after the previous dose.
- Concomitant medications and adverse events; and
- Study drug management:
    - For patients randomized to relugolix,
        - Perform study drug accountability.

6.4. Follow-up Period

The study day in which the Follow-up visit occurs is relative to when the patient takes his last dose of study drug. The End of Treatment is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.

30-Day Safety Follow-up Visit (Visit Window ± 7 Days)

A Safety Follow-up visit should occur 30 days after the End of Treatment and may occur earlier for patients who are starting alternative androgen deprivation therapy or do not complete 12 weeks of study treatment. Adverse events should continue to be collected and recorded through 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Serious adverse events and concomitant medications will be collected from the signing of the informed consent form until the Safety Follow-up visit approximately 30 days after the last dose of study drug.

All other study procedures should be completed before the start of alternative androgen deprivation therapy.

The following assessments will be performed:

- Patient-reported questionnaires
    - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs and weight;
- 12-lead ECG;
- ECOG performance assessment;
- Symptom-based physical examination;
- Laboratory collection (see Section 1.1); and
- Concomitant medications and adverse events.

Testosterone Recovery Visit (Visit Window ± 7 Days)

Patients who have started alternative androgen deprivation therapy will not participate in the 60- and 90-day follow-up visits. Approximately 100 patients randomized to receive relugolix and approximately 50 patients randomized to receive leuprolide acetate who complete the 48 weeks of study drug treatment and, in the opinion of the investigator, are candidates for intermittent androgen deprivation therapy will be included in the Testosterone Recovery 60- and 90-day Follow-up visits. These patients will discontinue relugolix after 48 weeks of treatment and will be offered a period off androgen deprivation therapy.

The following assessments will be performed:

- Patient-reported outcome questionnaires
  - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs;
- Symptom-based physical examination;
- Laboratory collection (see Section 1.1); and
- Concomitant medications.

Health Status Survey

During the final weeks prior to database lock, sites will be asked to contact all study participants or their immediate family regarding the current health status of previously enrolled/completed study patients. If the site is unsuccessful in contacting the patient and/or immediate family, the site may access hospital records or publicly available sources such as national registries, newspaper obituaries, and social networking websites.

6.5. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The following activities should be completed at an Unscheduled visit: recording of the date and reason for the visit in the patient's source documents, concomitant medication review and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment and collection of a PK sample if indicated, 12-lead ECG, study drug compliance and dispensation, etc. may be conducted as needed. See Schedule of Events (see Section 1.1) for tests that may be performed if indicated at an unscheduled visit. Consult with the medical monitor, if needed, to discuss Unscheduled visit testing.

6.6. Study Procedures

6.6.1. Efficacy-Related Procedures

6.6.1.1. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, testosterone, dihydrotestosterone, sex hormone binding globulin, and PSA will be collected predose at the visits indicated in the Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. Testosterone samples may be analyzed at a second laboratory to confirm non-castrate levels (Section 1.1).

Serum LH, FSH, dihydrotestosterone, sex hormone binding globulin, and PSA samples will be analyzed at a central laboratory.

PSA will also be used to evaluate biochemical progression per Prostate Cancer Clinical Trials Working Group 3 guidelines [Scher, 2016].

Analysis of serum samples for testosterone is detailed below:

Testosterone Assessment

Serum concentrations of testosterone will be obtained as indicated in the Schedule of Activities (see Section 1.1).

Testosterone will be assayed using a liquid chromatography-tandem mass spectrometry method sensitive at least as low as 5 ng/dL (0.17 nmol/L) for all measurements.

Between Week 5 and Week 49 visits (inclusive), testosterone samples that are above castrate level (> 50 ng/dL) will be reported to the investigator at the respective study site. Testosterone samples may be subject to reanalysis by liquid chromatography/mass spectrometry and/or immunoassay sensitive to at least as low as 10 ng/dL.

Instructions for collection and processing of blood specimens are provided in the investigator site file.

6.6.1.2. Pharmacokinetic Sample Collection

Relugolix

Pharmacokinetic samples will only be collected in patients randomized to relugolix study drug.

Blood samples for pharmacokinetic analysis of relugolix will be collected at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients may take their dose of study drug in the clinic at these visits. Study drug will be administered on an empty stomach or at least 2 hours before food, and food will be withheld for 1 hour after dosing. The date and time of their previous dose of study drug (ie, the dose the day before the clinic visit) will be accurately recorded.

Ideally, predose samples should be collected approximately 24 hours (±6 hours) after the previous dose of relugolix, although samples collected outside of this window would not be considered a protocol deviation.

If the study patient inadvertently took the study drug at home on the morning of the clinic visit, the date and time of that dose should also be accurately recorded and the pharmacokinetic sample collected, which may be used for population PK modeling.

Plasma from the Week 5 and Week 13 visits in all patients will be analyzed for relugolix plasma concentration. Analysis of other individual patient plasma samples will be performed on a case-by-case basis (such as those patients with non-castrate testosterone levels).

Collection, processing, storage, and shipping instructions will be provided in the investigator site file. Plasma analysis of relugolix will be performed by the sponsor (or designee).

Leuprolide Acetate

For patients on leuprolide acetate, in the event of non-castrate testosterone levels, a blood sample may be taken for potential analysis of leuprolide acetate plasma concentration, following discussion with the medical monitor

China and Japan Pharmacokinetic Subset

In a subset of patients from China (if enrolled) and approximately 20 patients from Japan that are randomized to relugolix, additional relugolix PK samples will be collected on Day 1, Day 4, and Week 2 visits (see Schedule of Activities in the protocol synopsis, Section 1.1). The actual date and time of study drug administration and the date and time of each PK sample will be accurately recorded.

All samples from the China and Japan subset will be analyzed for plasma relugolix concentrations. Collection, processing, storage, and shipping instructions will be provided in the investigator site file. Plasma analysis of relugolix will be performed by the sponsor (or designee).

6.6.1.3. Pharmacogenomics Sample Collection

Whole Blood Sample for Germline Deoxyribonucleic Acid

Pharmacogenomic analysis may be conducted to examine the contribution of genetic variance on drug response, for example, its efficacy and safety. Participation of study patients in pharmacogenomic sample collection is optional. A pharmacogenomics sample will be collected from patients at all participating study centers, with individual patient consent and per local ethics and regulatory standards. The sample will be retained for germline deoxyribonucleic acid (DNA) analysis of potential genetic determinants of drug safety, drug efficacy or disease response, and drug metabolism.

Every patient must sign informed consent/be consented in order to participate in the sampling of whole blood for DNA analysis. This research may be used to develop a better understanding of the safety and efficacy of relugolix and other study drugs, to increase understanding of the disease/condition being studied, and for improving the efficiency, design and study methods of future research studies.

Two venous whole blood sample (4 mL per sample) for the analysis of germline DNA will be collected at Day 1 from all patients who have provided informed consent. The DNA samples are expected to be collected at the Day 1 visit, but if necessary, may be collected at any visit after randomization. If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible. Germline DNA analysis may be conducted to investigate the contribution of genetic variance on drug response, for example, its efficacy and safety. As pharmacogenomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples.

Individual blood samples for germline DNA analysis, including the result of any analyses and corresponding information will be identified only by a code in a computer database.

The whole blood samples for DNA analysis will be stored securely at the sponsor's location or its designated central laboratory vendor until 10 years after completion of this study (HERO, MVT-601-3201) and/or until the drug development of relugolix is no longer actively pursued by Myovant or its collaborators. The storage period for these samples may be adjusted by country in accordance with local regulatory and/or legal requirements for the storage of research samples.

Such changes will be reflected in the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) country-specific informed consent form. After that time, the samples will be properly destroyed by the central laboratory or designee following approval by the sponsor. The investigator will keep records linking the patient identity with the samples for the time required by applicable law. Patients who consent and provide a pharmacogenomic sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time.

Directions for sample collection and handling can be found in the investigator site file.

6.6.1.4. Quality of Life

European Quality of Life 5-Dimension 5-Level Assessment

The EuroQol EQ-5D-5L comprises 5 scales and an overall assessment of health status on a visual analogue scale (Appendix 2). The 5 scales include: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The original version, the EQ-5D-3L, includes 3 response options for each scale. However, a new 5-level response-option version, the EQ-5D-5L, has been developed with the following response options: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. It is believed that the EQ-5D-5L is superior to the EQ-5D-3L in terms of feasibility, ceiling effects, discriminatory power, and convergent validity. The EQ-5D-5L index values will be calculated from the EQ-5D-5L descriptive system scores based on the Crosswalk value sets [EuroQol Group, 1990; Brooks, 1996; Herdman, 2011; Janssen, 2013].

European Organisation for Research and Treatment of Cancer Assessments

The EORTC-QLQ-C30 [Fayers, 2001; Fayers, 2002] (Appendix 3) and the 25-item prostate cancer module EORTC-QLQ-PR25 [Spry, 2006] (Appendix 4) will be administered as specified in the Schedule of Activities (see Section 1.1).

The EORTC QLQ-C30 core measurement will be used to capture distal outcomes, including physical, social functioning, and overall health-related quality of life. The QLQ-C30 core questionnaire incorporates 30 questions comprising 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality of life scale. Several single-item symptom measures are also included. It is a reliable and valid measure of health-related quality of life in patients with cancer and takes about 11 minutes to administer. The instrument has been validated and used in many countries [Aaronson, 1993].

The EORTC-QLQ-PR25 is the 25-item Prostate Cancer module (P25) of the EORTC. The EORTC-QLQ-PR25 contains 3 additional symptom scales (urinary, bowel, sexual) and 5 treatment-related items.

6.6.2. Safety-Related Procedures

6.6.2.1. Weight, Height, and Body Mass Index

Height and weight will be measured during screening (within 28 days before the first dose of study drug). Weight will be obtained at additional time points as specified in the Schedule of

Activities (see Section 1.1). Patients should have weight and height measured while wearing indoor clothing and with shoes removed.

6.6.2.2. Vital Signs

Vital sign measurements include temperature, pulse rate, and seated measurement of diastolic and systolic blood pressure. For each patient, temperature should be recorded using the same modality throughout the entire study. Patients should be sitting at rest for 5 minutes before blood pressure is measured. When vital sign measurements are scheduled at the same time as an ECG and blood draw, the vital signs, when possible, will be obtained immediately prior to the ECG and blood draw, and the blood draw will be collected at the scheduled time.

6.6.2.3. Physical Exams and Visual Acuity

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart, and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the baseline assessment.

Visual acuity will be evaluated at Screening, Week 25, and Week 49 by a standard visual eye chart. Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, he should wear his usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions (see the investigator site file for additional details).

Patients whose presenting visual acuity score is 90 or lower at the screening visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, i.e., an ophthalmologist or an optometrist. Any findings (i.e., diagnoses) from the eye examination should be recorded as medical history.

Patients whose presenting visual acuity score at Week 25, Week 49, or Early Termination has decreased by 10 or more points from the screening visit must be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.

6.6.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the investigator site file and the protocol Schedule of Activities (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the patient ID number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Metabolic Panel**
Hematocrit Hemoglobin Leukocytes with differential Neutrophils and absolute neutrophil count Platelet (count)	Albumin Alkaline phosphatase ALT AST Bilirubin (total) Blood urea nitrogen Calcium Carbon dioxide Creatinine Chloride Serum gamma-glutamyl transferase Glucose Lactate dehydrogenase Magnesium Phosphate Potassium Sodium Urate	Total cholesterol High density lipoprotein cholesterol Low density lipoprotein cholesterol Triglycerides Hemoglobin A1c
Endocrine Panel	**Diagnostic Screening (investigator's discretion)**	
Serum testosterone Serum LH Serum FSH Serum sex hormone binding globulin	Hepatitis panel, according to CDC criteria	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FSH, follicle-stimulating hormone; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; LH, luteinizing hormone

A separate sample will be collected at the Day 1 visit and will be banked and tested for presence of hepatitis A, B, and C (hepatitis A antibody, IgM, hepatitis B core antibody, IgM, hepatitis B surface antigen, and hepatitis C antibody) if requested by the medical monitor for evaluation of abnormal liver function tests.

The central laboratory will perform laboratory tests for chemistry, hematology, and plasma and serum hormone levels.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

6.6.2.5. 12-Lead Electrocardiograms

A 12-lead ECG will be administered at the time points specified in the Schedule of Activities (Section 1.1). When an ECG is scheduled at the same time as vital signs and a blood draw, the ECG, when possible, will be obtained after the vital signs and prior to the blood draw; the blood draw will be collected at the scheduled time. ECGs will be read locally by a qualified physician.

If patients have a prolonged QTc (> 500 msec) in the absence of a pacemaker, the ECG should be repeated and confirmed. Patients with a confirmed QTc > 500 msec, measured by Fridericia's formula [QTcF = QT/(RR^0.33)], should be withdrawn. All abnormal ECG findings must be documented by the investigator as clinically significant or not.

6.6.2.6. Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient 30 days prior to the first dose of study drug until 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection will recorded in the eCRF (Exception: amiodarone will be reported if taken within 3 months prior to the first day of study drug). See Section 5.10.1 for a list of medications and therapies that are prohibited and/or allowed during the study.

6.6.2.7. Radiologic Assessment

CT imaging or MRI of the abdominopelvic region with contrast and a bone scan must be obtained prior to randomization for each patient to determine the presence or absence of metastatic disease. The scans should be read locally and do not need to be repeated if a scan exists within 60 days prior to the Baseline Day 1 visit. However, if CT or MRI demonstrates presence of metastatic disease, a bone scan is not required. If metastatic disease is not present on CT or MRI, then a bone scan is also required.

Radiologic assessment is not included as part of the Schedule of Activities after randomization.

6.7. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of 8 mL of whole blood for pharmacogenomics testing (see Section 6.6.1.3) will be collected.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of his sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations including visual acuity assessment, vital signs, weight, ECGs, and clinical laboratory tests.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention; or
    - Requires interruption or discontinuation of study drug.

Events that **do not** meet the definition of an adverse event include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- The disease/disorder being studied, or expected progression;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen; and
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent).

Adverse events that occur during the study should be evaluated by the investigator and graded according to CTCAE (Appendix 5). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous". Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of study drug are permitted; however, study drug can be held for a period of up to 10 days for evaluation

and treatment of an adverse event. The study drug may be restarted if deemed safe for the patient by the investigator.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events that jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local IRB/IEC.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's answers to the EQ-5D-5L will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in a partner will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered until the Safety Follow-up visit approximately 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first.

Serious adverse events will be collected from the signing of the informed consent form until the Safety Follow-up visit approximately 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

Any event occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who

continues to meet eligibility criteria and proceeds to dosing with study drug; the exception to this includes procedure-related pretreatment-emergent events which should be recorded as adverse events in the electronic data capture (EDC) system for those patients who remain eligible for study participation.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The definitions in Table 7-1 are to be used for the relationship of the adverse event to study drug.

Table 7-1 Causal Relationship to Study Drug

Relationship	Criteria
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (re-challenge) or withdrawal (de-challenge).
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE (see Appendix 5). For terms not specified with the CTCAE, the criteria in Table 7-2 should be used to determine the grade severity.

Table 7-2 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized Treatment Period or the Follow-up visit should be reported to the sponsor using the serious adverse event form within 24 hours of the study site personnel's knowledge of the event (see Section 7.6), even if the event does not meet serious adverse event criteria. Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 6.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or international normalized ratio (INR) >1.5
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1) AST or ALT increases to ≥ 3 x ULN; AND
2) Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3) Alkaline phosphatase value does not reach 2 x ULN; AND
4) No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease;
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus);
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
   - Alcoholic hepatitis;
   - Nonalcoholic steatohepatitis; or
   - Autoimmune hepatitis.

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

Using a serious adverse event report form, all serious adverse events must be reported **within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose or pregnancy of partner is available on the serious adverse event report form and is as follows:

Send completed Safety Report Forms to IQVIA (previously named QuintilesIMS; contact information as below and on the SAE Form):

Site Location	E-mail (Primary reporting method)	Fax Number (Secondary reporting method)
All Regions	PPD	PPD

For questions on Serious Adverse Event (SAE)/Adverse Event of Clinical Interest or events of overdose reporting, please call:

- North/South America: PPD
- Regional toll-free phone and fax lines distributed separately. Please refer to the investigator site file.

The initial report should include:

- Study number (MVT-601-3201);
- Site address and number;
- Investigator name;
- Patient ID number, sex, and age;
- Details of study drug administration;
- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity); and
- Causal relationship to the study drug.

If the patient died, the report should include the cause of death and whether or not the cause of death was related to study drug, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 240 mg within a 24-hour window is an overdose, except for the 360-mg loading dose. The sponsor does not recommend specific treatment for an overdose; supportive treatment should be provided as clinically applicable.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis); and

- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If the partner of any patient becomes pregnant during the study or through 4 months after the last dose of study drug, the investigator must inform the sponsor of the pregnancy.

The patient should remain on study drug treatment, unless otherwise indicated.

If the patient agrees, the patient's pregnant partner should be notified and requested to sign a Release of Information form, permitting transfer of information regarding the pregnancy and outcome to the sponsor.

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the partner pregnancy report forms. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Benefit/Risk Assessment

Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

The risk assessment and mitigation strategies for this protocol are outlined in Table 7-3.

Table 7-3 Relugolix Potential Risks and Mitigation

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Stopping Criteria**
Hepatic Enzyme Increases Isolated increases in hepatic enzymes have been observed in prior clinical studies. Hepatic enzyme increases, considered an important potential risk of treatment with relugolix, are closely monitored in accordance with FDA guidelines for assessing drug-induced liver injury [FDA, 2009] in all relugolix studies.	Exclusion criteria for AST and ALT > ULN; total bilirubin values > ULN unless consistent with Gilbert's syndrome.	Liver chemistry will be monitored during the study. Appropriate liver stopping criteria and follow-up procedures are detailed in Section 7.5.2.
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Stopping Criteria**
evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.		acuity will be evaluated during the study.
Risks Associated with Medical Castration Acute and subsequent chronic symptoms of medical castration (reduction of testosterone to ≤ 50 ng/dL [1.7 nmol/L]) include vasomotor symptoms or hot flushes, disturbed sleep related to vasomotor symptoms, decreased libido, and fatigue or loss of energy. These side effects are usually not severe and can be managed with anticipatory guidance. Long-term suppression of testosterone is associated with well-characterized risks including bone loss, decreased muscle mass, possible changes in insulin sensitivity with increased risk of diabetes, altered lipid metabolism, and possible increased risk of cardiovascular disease [Oefelein, 2002; Lopez, 2005; Diamond,1998; Keating, 2006; Braga-Basaria, 2006; Saigal, 2007; Tsai, 2007; D'Amico, 2007; Efstathiou, 2009].	-	Effects can usually be managed with appropriate anticipatory guidance (eg, diet and exercise programs) or supportive therapy when required (eg, lipid-lowering or bone-sparing agents).
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	-	Fasting lipids and glucose will be monitored during the study.
Loss of Bone Mineral Density Loss of bone mineral density is considered a potential risk of treatment with relugolix in the prostate cancer indication.	-	Fractures will be assessed through adverse event monitoring. Use of anti-resorptive bone therapy, such as bisphosphonates or denosumab, may be considered by the treating physician.

Abbreviations: ALT; alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; FDA, Food and Drug Administration; PLD, phospholipidoses; ULN, upper limit of normal

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the investigator site file with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and Good Clinical Practices. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

8.3. Independent Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will review available safety data, as appropriate, on a periodic basis throughout the conduct of the study. Details of the Data and Safety Monitoring Board will be captured in a charter prior to the start of the study.

8.4. Steering Committee

A Steering Committee consisting of experts in the field of prostate cancer and staff members of Myovant Sciences GmbH will be established to provide oversight for the clinical trial, study design, study conduct, data analysis, and presentation and publication of the study data. Details of the Steering Committee responsibilities will be captured in a separate charter.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan will describe the detailed statistical methods and analyses for this study. The statistical analysis plan will be prepared and finalized prior to database lock and analysis of the primary and secondary endpoints.

All confidence intervals will be 2-sided at an alpha level of 0.05 unless otherwise specified. The methodology to be used to maintain a study-wide type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 2:1, relugolix to leuprolide acetate 3-M depot. Randomization will be stratified by the following factors:

- Geographic Region: North and South America versus Europe versus Asia and Rest of World;
- Presence of Metastatic Disease: yes versus no;
- Baseline Age: $\leq$ 75 years old versus > 75 years old.

Stratified efficacy analyses will incorporate these 3 stratification factors unless otherwise specified.

9.2. Analysis Populations

The Intent-To-Treat (ITT) population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. This will be the primary population used for the efficacy analysis. Patients will be analyzed according to their randomized treatment assignment.

The Per-Protocol population will consist of those members of the ITT population who have no major protocol deviations as defined in the statistical analysis plan, considering the following protocol deviations but not limited to:

- Those who entered the study even though they did not satisfy the entry criteria;
- Those who developed withdrawal criteria during the study but were not withdrawn;
- Those who received the wrong treatment or incorrect dose;
- Those who received an excluded concomitant treatment.

The Per-Protocol population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT population. The Per-Protocol population will be used as a sensitivity analysis of the ITT population for the primary efficacy endpoint and secondary endpoints. The Per-Protocol population will be identified prior to the database lock.

The primary population for safety analyses will be the Safety population, defined as all patients who receive at least one dose of any study treatment. Patients will be analyzed according to the treatment actually received, regardless of their randomized treatment assignment.

9.3. Efficacy Analyses

9.3.1. Primary Endpoint Analyses

The primary efficacy endpoint is the sustained castration rate, defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 (Study Day 337). This probability will be estimated for each treatment group using the Kaplan-Meier method with the confidence interval calculated using the exponential Greenwood formula via log-log transformation of the survival function. Patients who discontinue treatment prior to observing a testosterone level > 50 ng/dL (1.7 nmol/L) will be censored at the last testosterone assessment prior to discontinuation. Detailed censoring rules will be described in the statistical analysis plan.

There are 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit:

- Evaluation Criterion 1: to determine whether the sustained castration rate for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion.
- Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion. The confidence interval of the treatment difference will be calculated using the formula $\hat{V}\left[\widehat{S_1}(t) - \widehat{S_2}(t)\right] = \hat{V}\left[\widehat{S_1}(t)\right] + \hat{V}\left[\widehat{S_2}(t)\right]$, where each of the variance of the Kaplan-Meier estimate will be calculated using the Greenwood's formula $\hat{V}\left[\hat{S}(t)\right] = \hat{S}(t)^2 \left[\sum_{j:t_{(j)} \le t} \frac{d_j}{n_j(n_j - d_j)}\right]$; n_j denote the number of patients at risk at time $t_{(j)}$ and d_j denote the number of events observed at time $t_{(j)}$) [Lachin, 2000].

The evaluation criteria used for the primary efficacy endpoint assessment will be determined by regional regulatory requirements and will be prespecified in separate regional statistical analysis plans. The 2-sided type I error rates for the final analyses will be controlled at 0.05 separately for each regional analysis.

9.3.2. Secondary Endpoint Analyses

If the result of the primary endpoint is statistically significant, the secondary endpoints will be analyzed. The methods and procedures necessary to maintain a study-wide 2-sided type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

- Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing at Week 1 Day 4, and prior to dosing at Week 3 Day 1 will be summarized by treatment group using the Kaplan-Meier method;
- Profound castration rate defined as the cumulative probability of testosterone suppression of ≤ 20 ng/dL (0.7 nmol/L) while on treatment from Week 25 Day 1 through Week 49 Day 1 will be estimated for each treatment group using the Kaplan-Meier method. The difference in the cumulative probabilities between the relugolix group and the leuprolide acetate group will be provided, along with the 95% confidence interval calculated in the same manner as in the primary analysis of the primary endpoint;
- PSA response and percent change from baseline in PSA at Week 3 and Week 5 will be summarized and compared between the relugolix group and the leuprolide acetate group;
- Proportions of patients who have a PSA concentration < 0.2 ng/mL (0.2 µg/L) at Week 25 will be summarized by treatment group. The proportions will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in proportions;
- Time to testosterone recovery in approximately 100 patients randomized to relugolix and approximately 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last received leuprolide acetate 3-M depot injection) will be compared between the relugolix group and the leuprolide acetate group;
- Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains will be summarized by treatment group. The least square means at Week 49 will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in the least square means using a mixed model for repeated measures;
- Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as EQ-5D-5L will be summarized by treatment group. The least square means at Week 49 will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in the least square means using a mixed model for repeated measures; and
- Time to PSA progression;
- Proportion of patients with confirmed PSA progression among those who have achieved sustained testosterone suppression during the 48-week treatment.

Further details of the secondary analyses will be described in the statistical analysis plan.

9.4. Safety Analyses

The safety analyses will be based on the Safety population. Safety will be assessed by summarizing and analyzing adverse events, laboratory analytes, vital signs, ECG parameters, and concomitant medications.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ class using MedDRA 19.1 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used for analyses. The National Cancer Institute CTCAE will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the baseline versus post-baseline results.

9.5. Pharmacokinetic Analyses

Plasma relugolix concentrations will be listed and summarized and included in the clinical study report.

PK data may be pooled with data from other studies in healthy male patients and patients with prostate cancer for population PK analysis, including evaluation of covariates of relugolix PK parameters, and for input into a population PK/pharmacodynamics models describing the relationship between relugolix exposure and serum testosterone [Ahsman, 2016]. These population PK analyses will be detailed further in a separate statistical analysis plan and report.

For patients from China (if enrolled) and Japan in the PK subset, plasma relugolix PK parameters C_{max}, $AUC_{0-\tau}$, and t_{max} from Day 1 and Day 14 of dosing will be determined. Population PK or PK/pharmacodynamic analyses may be conducted to explore the factors that affect relugolix exposure or to contribute to the assessment of the relationships between exposure and testosterone.

9.6. Endocrine Marker Analyses

Endocrine markers will be analyzed to see effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for:

- LH at Day 4, Week 5, Week 25, and Week 49 visits and/or follow-up visit(s);
- FSH at Day 4, Week 5, Week 25, and Week 49 visits and/or follow-up visit(s);

- Dihydrotestosterone at Week 5, Week 25, and Week 49 visits and/or follow-up visit(s);
- Sex hormone binding globulin at Week 5, Week 25, and Week 49 visits and/or follow-up visit(s).

9.7. Exploratory Analyses

Overall survival: Overall survival defined as time from randomization to date of death prior to data cutoff date. Kaplan-Meier methods will be used to describe survival distributions for each treatment arm.

Pharmacogenomic analyses may be conducted to examine the contribution of genetic variance on drug response, for example, its efficacy and safety, pending availability of samples. Polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix. These analyses will be detailed in a separate statistical analysis plan and associated reports.

9.8. Interim Analyses

There will be no planned interim efficacy analysis for the study.

9.9. Sample Size

To calculate the sample size required for the primary efficacy endpoint of this study, the following assumptions have been made:

- True probabilities of sustained testosterone suppression are 94% and 96% for relugolix and leuprolide acetate, respectively;
- 2:1 randomization ratio (relugolix:leuprolide acetate); and
- Dropout rate of 15%.

The assumed probability of sustained testosterone suppression for relugolix arm is 94%. It was estimated based on the predicted dose-response relationship for the effect of relugolix on testosterone suppression in patients with prostate cancer (data from phase 2 studies C27002 and C27003). The assumed castration rate of 96% for leuprolide acetate was based on the results from degarelix phase 3 registration program [Shore, 2013].

For Evaluation Criterion 1, 610 patients in the relugolix group will provide approximately 90% power to rule out a fixed probability of sustained testosterone suppression of < 90% at a 2-sided type I error rate of 0.05.

For Evaluation Criterion 2, with the non-inferiority margin of -10% and an overall 2-sided type I error rate of 0.05, a total of approximately 915 patients (610 relugolix, 305 leuprolide acetate) will yield at least 99% power in declaring the non-inferiority of relugolix compared to leuprolide acetate.

The final analysis will be performed separately for individual evaluation criterion using data collected through 48 weeks after enrollment of approximately 915 patients.

Approximately 915 patients will be randomized in order to fulfill the regulatory requirements of all participating countries.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a US investigational new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) Part 312, subpart D, "Responsibilities of sponsors and investigators," 21 CFR Part 50, and 21 CFR Part 56, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR Part 54, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

A properly executed, written informed consent, in compliance with the Declaration of Helsinki, ICH Good Clinical Practice, US CFR for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27), and local regulations, will be obtained from each patient before entering the patient in the trial. The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

The investigator will provide copies of the signed informed consent form to each patient (or to the patient's legal representatives) and will maintain the signed original document within the patient's record file per local requirements. The investigator will also fully document the informed consent process in the patient's source records.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator Brochure, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories:

1) Investigator's study file: The investigator's study file will contain the Investigator Brochure, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents: The required source data should include the following for each patient:
   - Patient identification (name, date of birth, gender);

- Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
- Participation in the study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
- Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
- Concomitant medication (including start and end date); and
- Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the Investigator Brochure, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.5. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on the 1572 form and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization Screening Period if an eCRF was initiated). If a patient withdraws from the study, the reason

must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.6. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability including dates and lot numbers of all study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, patient ID number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

All records must be made available to the sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

Current ICH Good Clinical Practice guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (eg, pharmacist), and the following:

- That such deliveries are recorded, for example, on the sponsor-approved drug accountability log, or other sponsor-approved pharmacy log;
- That study drug is handled and stored safely and properly in accordance with the study protocol;
- That study drug is only dispensed to study patients in accordance with the protocol;
- That any unused study drug is returned to the sponsor-designated facility or standard procedures for the alternative disposition of unused study drug are followed and only after approval by the sponsor representative.

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drug to any persons except the patients in this study;
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs;

- The investigator/pharmacist will maintain a study drug inventory. The inventory will include details of material received and a clear record of when they were dispensed and to which patient;
- The investigator/pharmacist agrees to conduct a final drug supply inventory on the drug accountability record at the conclusion or termination of the study. It must be possible to reconcile delivery records with those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries must be signed by the person responsible;
- Used or unused study drug may be destroyed at the study site according to standard institutional procedures if the sponsor agrees with the procedure, and after drug accountability has been conducted by the sponsor or representative. Unused study drug not destroyed at the site must be returned to the sponsor-designated facility at the end of the study or upon expiration.

10.1.7. Inspections

During the course of the study and after study completion, it is likely that one or more quality assurance audits will be undertaken by authorized sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the protocol as well as recognized Good Clinical Practice guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed time. By signing this protocol, the investigator grants permission to the sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.8. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of

emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers (eg, http://www.clinicaltrials.gov) before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH Good Clinical Practice guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may terminate the study and send a written notice of the termination along with the reasons to the investigator. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants' interests.

If the investigator intends to terminate participation in the study, the investigator must immediately inform the sponsor and provide the reason to it.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

Ahsman M, Faessel HM, Snelder NS, MacLean D, Vis P. Modelling and simulation of oral GnRH Antagonist TAK-385 and testosterone-lowering response in Prostate Cancer Patients to Optimize Trial Design and Dose Selection. Population Analysis Group Europe. 2016; Abstr 5847. Available at: http://www.page-meeting.org/print_abstract.asp?abstract_id=5847. Accessed: 11 January 2017.

Bosland MC. Testosterone treatment is a potent tumor promoter for the rat prostate. Endocrinology. 2014 Dec;155(12):4629-33.

Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, Basaria S. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol. 2006 Aug 20;24(24):3979-83.

Brooks R. EuroQol: the current state of play. Health Policy. 1996 Jul;37(1):53-72.

Cersosimo RJ, Carr D. Prostate cancer: current and evolving strategies. Am J Health Syst Pharm. 1996 Feb 15;53(4):381-96; quiz 446-8.

Conn PM, Crowley WF Jr. Gonadotropin-releasing hormone and its analogues. N Engl J Med. 1991 Jan 10;324(2):93-103.

D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ, Lamb DS, Joseph D, Tai KH, Malone S, Ludgate C, Steigler A, Kantoff PW. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol. 2007 Jun 10;25(17):2420-5.

Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. Cancer. 1998 Oct 15;83(8):1561-6.

Efstathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, Smith MR. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. J Clin Oncol. 2009 Jan 1;27(1):92-9.

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, et al. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: EORTC; 2001.

Fayers P, Bottomley A; EORTC Quality of Life Group; Quality of Life Unit. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur J Cancer. 2002 Mar;38 Suppl 4:S125-33.

FDA Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf. Accessed: 11 January 2017.

Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol. 2007 Mar;18(3):581-92.

Firmagon (degarelix for injection). Prescribing Information. Ferring Pharmaceuticals Inc., Parsippany, NJ, USA. Revised 07/2016. Available at: http://firmagon.com/. Accessed: 12 January 2017.

Foundation for Promotion of Cancer Research. Cancer Statistics in Japan-2012. December 2012.

Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA Cancer J Clin. 2001 Jan-Feb;51(1):15-36.

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.

Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, Swinburn P, Busschbach J. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013 Sep;22(7):1717-27.

Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006 Sep 20;24(27):4448-56.

Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, Jensen JK, Olesen TK, Schröder FH. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int. 2008 Dec;102(11):1531-8.

Klotz L, O'Callaghan C, Ding K, Toren P, Dearnaley D, Higano CS, Horwitz E, Malone S, Goldenberg L, Gospodarowicz M, Crook JM. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. J Clin Oncol. 2015 Apr 1;33(10):1151-6.

Kreis W. Current chemotherapy and future directions in research for the treatment of advanced hormone-refractory prostate cancer. Cancer Invest. 1995;13(3):296-312.

Lachin J. Biostatistical Methods: The Assessment of Relative Risks. 2nd ed. Balding D, Cressie N, Fitzmaurice G, Johnstone I, Molenberghs G, Scott D, et al., editors: John Wiley & Sons, Inc.; 2010.

Limonata P, Montagnani Marelli M, Moretti RM. LHRH analogues as anticancer agents: pituitary and extrapituitary sites of action. Expert Opin Investig Drugs. 2001 Apr;10(4):709-20.

Loblaw DA, Mendelson DS, Talcott JA, Virgo KS, Somerfield MR, Ben-Josef E, Middleton R, Porterfield H, Sharp SA, Smith TJ, Taplin ME, Vogelzang NJ, Wade JL Jr, Bennett CL, Scher HI; American Society of Clinical Oncology. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive

metastatic, recurrent, or progressive prostate cancer. J Clin Oncol. 2004 Jul 15;22(14):2927-41.

Lopez AM, Pena MA, Hernandez R, Val F, Martin B, Riancho JA. Fracture risk in patients with prostate cancer on androgen deprivation therapy. Osteoporos Int. 2005 Jun;16(6):707-11.

Lupron Depot. Prescribing Information. AbbVie Inc., North Chicago, IL, USA. Revised 6/2016. Available at: http://www.lupron.com/prescribing-information.aspx. Accessed: 12 January 2017.

Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. J Urol. 2002 Sep;168(3):1005-7.

Prostap 3 DCS. Summary of Product Characteristics, Section 4.8. Takeda UK Ltd. Revised 16/03/2016. Available at: https://www.medicines.org.uk/emc/medicine/24680. Accessed: 12 January 2017.

Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS; Urologic Diseases in America Project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer. 2007 Oct 1;110(7):1493-500.

Schally AV, Coy DH, Arimura A. LH-RH agonists and antagonists. Int J Gynaecol Obstet. 1980;18(5):318-24.

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, Antonarakis ES, Beer TM, Carducci MA, Chi KN, Corn PG, de Bono JS, Dreicer R, George DJ, Heath EI, Hussain M, Kelly WK, Liu G, Logothetis C, Nanus D, Stein MN, Rathkopf DE, Slovin SF, Ryan CJ, Sartor O, Small EJ, Smith MR, Sternberg CN, Taplin ME, Wilding G, Nelson PS, Schwartz LH, Halabi S, Kantoff PW, Armstrong AJ; Prostate Cancer Clinical Trials Working Group. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016 Apr 20;34(12):1402-18.

Shore ND. Experience with degarelix in the treatment of prostate cancer. Ther Adv Urol. 2013 Feb;5(1):11-24.

Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014 Jan-Feb;64(1):9-29.

Spry NA, Kristjanson L, Hooton B, Hayden L, Neerhut G, Gurney H, Corica T, Korbel E, Weinstein S, McCaul K. Adverse effects to quality of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer. Eur J Cancer. 2006 May;42(8):1083-92.

Tolis G, Ackman D, Stellos A, Mehta A, Labrie F, Fazekas AT, Comaru-Schally AM, Schally AV. Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. Proc Natl Acad Sci U S A. 1982 Mar;79(5):1658-62.

Tombal B, Miller K, Boccon-Gibod L, Schröder F, Shore N, Crawford ED, Moul J, Jensen JK, Kold Olesen T, Persson BE. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus

leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol. 2010 May;57(5):836-42.

Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst. 2007 Oct 17;99(20):1516-24.

Waxman J, Man A, Hendry WF, Whitfield HN, Besser GM, Tiptaft RC, Paris AM, Oliver RT. Importance of early tumour exacerbation in patients treated with long acting analogues of gonadotrophin releasing hormone for advanced prostatic cancer. Br Med J (Clin Res Ed). 1985 Nov 16;291(6506):1387-8.

APPENDICES

Appendix 1. Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Note: Adapted from Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

Appendix 2. EuroQol EQ-5D-5L Questionnaire

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

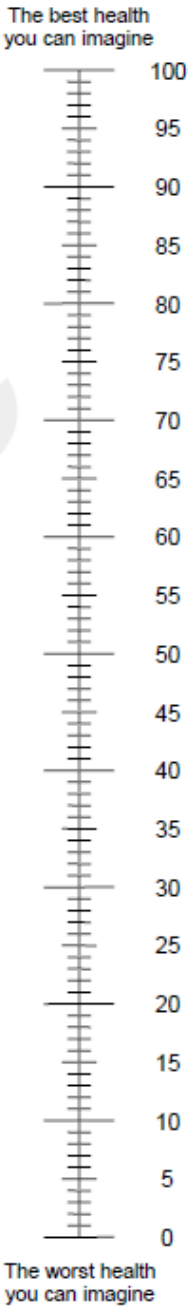
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 3. Quality of Life Questionnaire: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|

Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|

Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4. Quality of Life Questionnaire: EORTC QLQ-PR25

ENGLISH

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid: Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

ENGLISH

During the last 4 weeks:	Not at all	A little	Quite a bit	Very much
47. Has weight **loss** been a problem for you?	1	2	3	4
48. Has weight **gain** been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS:

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

Appendix 5. Adverse Event Severity Grading

When assessing adverse events, refer to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, June 14, 2010 (available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). A copy of the National Cancer Institute CTCAE table will be provided in the investigator site file.

The National Cancer Institute CTCAE is a descriptive terminology that can be utilized for adverse event reporting. A grading (severity) scale is provided for each adverse event term.

Components and Organization of the National Cancer Institute CTCAE

- System Organ Class (SOC). SOC, the highest level of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy, is identified by anatomical or physiological system, etiology, or purpose (eg, SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, adverse events are listed and accompanied by descriptions of severity (grade).
- CTAE Terms. Each CTCAE term is a MedDRA LLT (Lowest Level Term).
- Definitions. A brief definition is provided to clarify the meaning of each adverse event term.
- Grades. Grade refers to the severity of the adverse event. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each adverse event based on this general guideline:
    - Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
    - Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
    - Grade 4 Life-threatening consequences; urgent intervention indicated; and
    - Grade 5 Death related to adverse event.

      A semi-colon indicates “or” within the description of the grade. A single dash (-) indicates a grade is not available. Not all grades are appropriate for all adverse events. Therefore, some adverse events are listed with fewer than 5 options for grade selection.
- Grade 5. Grade 5 (Death) is not appropriate for some adverse events and therefore is not an option.

Appendix 6. Guidelines for Elevations in Hepatic Enzymes

Study drug treatment should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline. For this purpose, local labs can be used. However, duplicate samples should be taken for central analysis.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld, even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests[a,b]
If AST or ALT ≥ 3 x ULN **and** total bilirubin > 2 x ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 x ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions

b. Local labs can be used. However, duplicate samples should be taken for central analysis.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

- Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever);
- Prior and concurrent disease or illnesses;
- Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents;
- Prior and concurrent use of alcohol, recreational drugs, and special diets;
- Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms;
- Physical examination.

Recommended tests:

Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist.

- Repeat liver tests as per Appendix Table 1[a];
- Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests;
- Complete blood count with differential to assess for eosinophilia;
- Serum acetaminophen (paracetamol) concentration;
- Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus;
- Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc;
- Serology for celiac disease;
- Appropriate liver imaging; and
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

Abbreviations: INR, international normalized ratio

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

CLINICAL STUDY PROTOCOL

Study Title:	HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3201
Indication:	Advanced Prostate Cancer
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
IND Number:	118736
EudraCT Number:	2017-000160-15
Version / Effective Date:	Original: 13 January 2017 Amendment 1: 02 January 2018 Amendment 2: 18 January 2018
Study Medical Monitor:	PPD

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Myovant Sciences GmbH, and is provided to you in confidence as an investigator, potential investigator or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Myovant Sciences GmbH, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SPONSOR SIGNATURE PAGE

HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer

Protocol Number: MVT-601-3201

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

18-Jan-2018
Date

18-JAN-18
Date

18 JAN 2018
Date

18 JAN 2018
Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	**Signature**
Date	**Site**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
3-M	3-month
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
$AUC_{0-\tau}$	area under the concentration-time curve from time 0 to the end of the dosing interval
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DHT	dihydrotestosterone
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation of Research and Treatment of Cancer
EOT	end of treatment
EuroQol EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Questionnaire
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HbA1c	hemoglobin A1c
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
ICH	International Conference on Harmonization
ID	identification
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat (population)
IWRS	interactive voice/web recognition system
LH	luteinizing hormone
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

Term	Explanation
NOAEL	no-observed-adverse-effect-level
NYHA	New York Heart Association
Obs	observed
PK	pharmacokinetics
PLD	phospholipidosis
PSA	prostate-specific antigen
Q12W	once every 12 weeks
Q4W	once every 4 weeks
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QTc corrected using Fridericia's formula
SHBG	sex hormone binding globulin
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States

1. PROTOCOL SYNOPSIS

Study Title	HERO: A Multinational Phase 3, Randomized, Open-label, Parallel-group Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer
Protocol Number	MVT-601-3201
Location	Multinational, including North and South America, Europe, and Asia-Pacific
Study Centers	Approximately 200 sites
Study phase	Phase 3
Target Population	Men aged 18 or older diagnosed with androgen-sensitive advanced prostate cancer who are candidates for at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer and who are not be candidates for surgical therapy. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy.
Number of Patients Planned	Approximately 915 total patients
Study Objectives	Primary: • To evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) in men with androgen-sensitive advanced prostate cancer. Secondary: • To evaluate the time course and change in serum testosterone during treatment with relugolix; • To evaluate the time course and magnitude of prostate-specific antigen (PSA) reduction during treatment with relugolix; • To evaluate testosterone recovery following discontinuation of relugolix; • To evaluate quality of life using validated patient-reported outcome instruments; • To evaluate the safety of relugolix 120 mg once daily in men with androgen-sensitive advanced prostate cancer; • To evaluate the effect of relugolix and leuprolide acetate on endocrine pharmacodynamic parameters; • To collect relugolix plasma concentration data to further evaluate relugolix population pharmacokinetics (PK) and the relationship between relugolix exposure and serum testosterone; • To characterize the relugolix plasma PK parameters in a subset of patients from China (if enrolled) and Japan; and • To describe the time course and magnitude of PSA progression and

	development of castration resistant prostate cancer during treatment with relugolix. Exploratory: • To explore the overall survival of patients treated with relugolix; and • To explore the contribution of genetic variance on drug response.

Study Design

The HERO study is a phase 3 multinational randomized, open-label, parallel-group study to evaluate the safety and efficacy of relugolix in patients with androgen-sensitive advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy. Relugolix is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist that lowers testosterone by inhibiting pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Relugolix 120 mg orally once daily or leuprolide acetate depot suspension, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China), every 3-months (3-M) will be administered to patients with prostate cancer who require androgen deprivation therapy. This study will evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) for 48 weeks in patients with androgen-sensitive advanced prostate cancer.

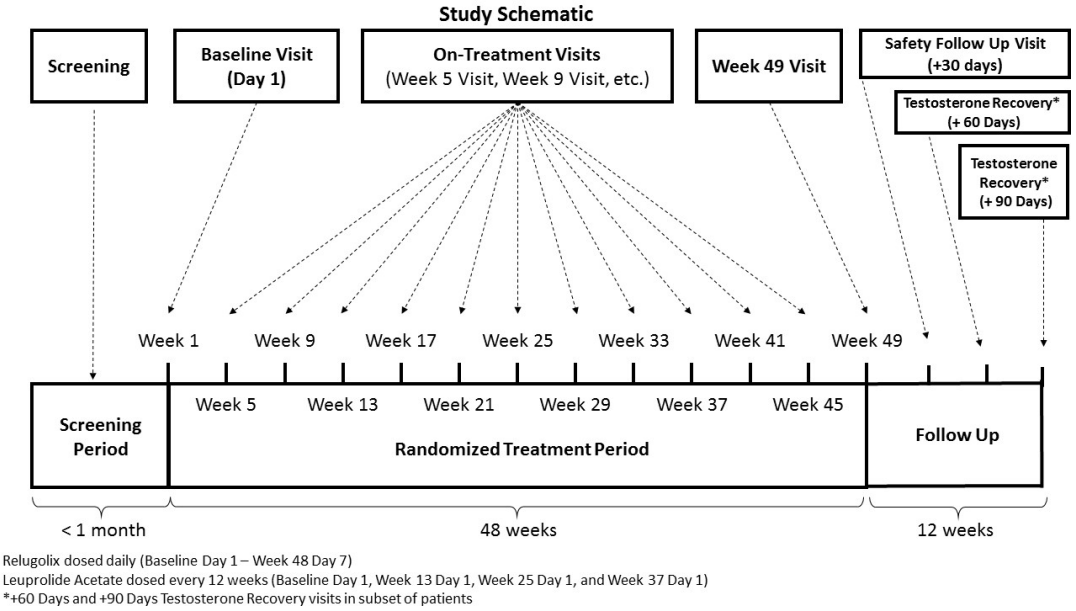
To be eligible for the study, a patient must be, in the opinion of the investigator, a candidate for at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer and must not be a candidate for surgical therapy. Eligible patients include those with evidence of biochemical relapse (rising PSA) following local primary intervention with curative intent, newly diagnosed metastatic disease (excluding metastases to the brain), and/or advanced localized disease. Patients may receive radiotherapy, cryotherapy or high frequency ultrasound no sooner than 2 months after initiation of androgen deprivation therapy. Patients may be included if they have not previously received androgen deprivation therapy for more than 18 months, and if the androgen deprivation therapy was completed at least 3 months prior to the baseline visit. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy. Baseline serum testosterone must be ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L) to be enrolled.

Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg once daily following a loading dose of 360 mg on Day 1 or 3-M depot of leuprolide acetate 22.5 mg (or 11.25 mg in Japan, Taiwan, and China). After randomization, patients on the leuprolide acetate arm may receive an antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator. Randomization will be stratified by geographic region, presence of metastatic disease, and age.

Approximately 915 patients will be enrolled in this study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region. The study includes a Screening Period of up to 28 days, a Treatment Period of 48 weeks, and a Follow-up Period of up to 90 days. Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed. Eligible patients will receive study treatment for 48 weeks. During that time, testosterone and PSA will be assessed monthly and patient-reported outcomes (European Organisation of Research and Treatment of Cancer [EORTC] QLQ-C30, European Quality of Life 5-Dimesion 5-Level questionnaire [EuroQol EQ-5D-5L]) will be

assessed approximately every 3 months during the Treatment Period and more frequently during the Follow-up Period. Additional serum endocrine evaluations will include: LH, FSH, dihydrotestosterone, and sex hormone binding globulin. Relugolix PK samples will be collected throughout the study. Full PK profiles will be determined in a subset of patients in China (if enrolled) and Japan. Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECG), and visual acuity tests.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (testosterone level ≤ 50 ng/dL [1.7 nmol/L]), should remain on study and may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide. For patients requiring other systemic antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.



Relugolix dosed daily (Baseline Day 1 – Week 48 Day 7)
Leuprolide Acetate dosed every 12 weeks (Baseline Day 1, Week 13 Day 1, Week 25 Day 1, and Week 37 Day 1)
*+60 Days and +90 Days Testosterone Recovery visits in subset of patients

Inclusion/Exclusion Criteria

Inclusion Criteria

All of the following inclusion criteria must have been met prior to randomization unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a male aged 18 years or older on the day of signing and dating the informed consent form;
3. Has histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate;
4. Is a candidate for, in the opinion of the investigator, at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer

with one of the following clinical disease state presentations:

a. Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, such as surgery, radiation therapy, cryotherapy, or high-frequency ultrasound and not a candidate for salvage treatment by surgery; or

b. Newly diagnosed androgen-sensitive metastatic disease; or

c. Advanced localized disease unlikely to be cured by - local primary intervention with either surgery or radiation with curative intent;

Note: radiotherapy, cryotherapy, or high frequency ultrasound are allowed after 2 months of androgen deprivation therapy.

5. Has a serum testosterone at the Screening visit of ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L);
6. Has a serum PSA concentration at the Screening visit of > 2.0 ng/mL (2.0 µg/L), or, when applicable, post radical prostatectomy of > 0.2 ng/mL (0.2 µg/L) or post radiotherapy, cryotherapy, or high frequency ultrasound > 2.0 ng/mL (2.0 µg/L) above the post interventional nadir;
7. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at initial screening and at baseline (refer to Appendix 1);
8. Is a male patient who, even if surgically sterilized (ie, status post vasectomy):

   a. Agrees to use a male condom if having sex with a woman of childbearing potential or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or

   b. Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception;

9. Must agree not to donate sperm from first dose of study drug through 4 months after the last dose of study drug;
10. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

1. In the investigator's opinion, is likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating androgen deprivation therapy;
2. Previously received GnRH analog or other form of androgen deprivation therapy (estrogen or antiandrogen) for > 18 months total duration. If androgen deprivation therapy was received for ≤ 18 months total duration, then that therapy must have been completed at least 3 months prior to baseline. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot;
3. Previous systemic cytotoxic treatment for prostate cancer (e.g. taxane-based regimen);
4. Metastases to brain per prior clinical evaluation;

5. *Removed;*
6. Scheduled for major surgery after baseline;
7. History of surgical castration;
8. Active malignancy beyond prostate cancer ***with the exception*** of any of the following:
   - Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ carcinoma of any type;
   - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for ≥ 2 years;
   - Any other cancer from which the subject has been disease-free for ≥ 5 years;

   The medical monitor should be contacted for any questions regarding this exclusion criterion;
9. Abnormal laboratory values at the Screening visit that suggest a clinically unstable underlying disease, or the following laboratory values:
   a. Serum gamma-glutamyl transferase > 2.0 x upper limit of normal (ULN);
   b. Serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > ULN;
   c. Total bilirubin > ULN (unless secondary to Gilbert's syndrome or the pattern is consistent with a diagnosis of Gilbert's syndrome);
   d. Serum creatinine > 2.0 mg/dL (176.8 µmol/L);
   e. Platelets < 100 x 10^3/µL or history of bleeding disorder;
   f. Hemoglobin < 10.0 g/dL (100 g/L);
   g. Leukocytes (WBC) < 3 x 10^3/µL (3 GI/L); or
   h. Absolute neutrophil count < 1.5 x 10^3/µL (1.5 GI/L);
10. Hemoglobin A1c (HbA1c) > 10% in patients previously diagnosed with diabetes mellitus. HbA1c > 8% in patients whose diabetes mellitus is previously undiagnosed. (Excluded patients may be rescreened after referral and evidence of improved control of their condition);
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (hepatitis A virus immunoglobulin M [IgM] positive), hepatitis B (hepatitis B virus surface antigen [HBsAg] positive), or hepatitis C (hepatitis C virus [HCV] antibody positive, confirmed by HCV ribonucleic acid);
12. Known human immunodeficiency virus infection;
13. Any of the following within 6 months before Baseline Day 1:
    a. Myocardial infarction;
    b. Unstable angina;
    c. Unstable symptomatic ischemic heart disease;
    d. New York Heart Association (NYHA) class III or IV heart failure;
    e. Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events);

f. Any other significant cardiac condition (e.g., pericardial effusion, restrictive cardiomyopathy, severe untreated valvular stenosis, or severe congenital heart disease);

14. The following ECG abnormalities are excluded:

    a. ECG evidence of acute ischemia;

    b. Q-wave infarction, unless identified 6 or more months before the Screening visit;

    c. QT interval corrected for heart rate (QTc) > 470 msec, measured by Fridericia's formula [QTcF = QT/(RR^0.33)]. If the QTc is prolonged in a patient with a pacemaker, the patient may be enrolled in the study if confirmed by the medical monitor; or

    d. Congenital long QT syndrome;

    e. Active conduction system abnormalities. Examples of active conduction system abnormalities include the following:

    - Mobitz II second degree heart block without a permanent pacemaker in place;
    - Third degree heart block without permanent pacemaker in place;
    - Untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    - Clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes;
    - Uncontrolled atrial fibrillation (patients with chronic stable atrial fibrillation on stable anticoagulant therapy or patients with stable cardiac rhythm controlled by a pacemaker are allowed);

    The following exceptions are allowed: First degree atrioventricular (AV) block, second degree AV block Type 1 (Mobitz Type 1/Wenckebach type), or right bundle branch block.

15. Uncontrolled hypertension despite appropriate medical therapy (sitting blood pressure of greater than 160 mmHg systolic and/or 100 mmHg diastolic at 2 separate measurements no more than 45 minutes apart during the Screening visit). Patients may be re-screened after referral and further management of hypertension;

16. Hypotension, as indicated by systolic blood pressure < 84 mmHg on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming upright position;

17. Bradycardia as indicated by a heart rate of < 45 beats per minute on the ECG at the Screening or Baseline Day 1 visit;

18. Treatment with any investigational product within 28 days or 5 half-lives (whichever is longer);

    Exception: treatment for prostate cancer with any investigational products where the mechanism of action is testosterone lowering. In this circumstance, there must be a minimum 12-month treatment free interval;

19. *Removed*;

20. Previous treatment with relugolix in a clinical study;

21. Patient is a study site employee or is a primary family member (spouse, parent, child, or

sibling) of a site employee involved in the conduct of the study; 22. Known gastrointestinal disease or procedure that could interfere with the oral absorption or tolerance of relugolix, including inability to swallow whole tablets or conditions that may interfere with absorption at the level of the small intestine. Examples of such conditions include but are not limited to Crohn's disease, gastric bypass, active peptic ulcer disease, and gastrectomy. The medical monitor should be contacted for any questions regarding this exclusion criterion; 23. Use or planned use of any medication listed in the prohibited medications table (see Section 5.10.1) without the appropriate washout period; 24. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation; 25. Has a prior (within 1 year of the Screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form [eCRF]); 26. Any other medical or psychiatric condition that, in the opinion of the investigator, would interfere with completion of treatment according to this protocol. 27. Weight ≥ 400 pounds (181 kg) or has a body mass index ≥ 50;	
Dose and Route of Administration	Test Product Relugolix 120 mg tablet strength will be available as immediate-release film-coated tablets, and 1 tablet (120 mg) will be administered once daily following an oral loading dose of 360 mg (three 120-mg tablets) on Day 1. These tablets will be presented in 45-tablet bottles and dispensed to patients every 4 weeks at scheduled study visits. All protocol-specific inclusion criteria and none of the exclusion criteria must be met and documented prior to study drug administration. Study drug will be dispensed only to eligible patients who are under the supervision of the investigator or identified subinvestigator(s). Reference Product Leuprolide acetate, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China), 3-M depot will be administered per the approved dose and method of dosing in the region where the patient is enrolled. Leuprolide acetate 3-M depot injection will be administered on Day 1 (with an antiandrogen of choice, if indicated according to the investigator, for the first 4 weeks or longer), then at 12-week intervals thereafter for 48 weeks. Preparation of the depot injection and administration should follow the instructions provided by the manufacturer.
Duration of Treatment	The duration of treatment will be 48 weeks. The last dose of leuprolide acetate 3-M depot will be administered at the Week 37 visit.
Criteria for Evaluation	The following treatment arms will be evaluated after 48 weeks of study treatment: • Arm A: Oral relugolix 120 mg once daily following a loading dose of

	360 mg (three 120-mg tablets) on Day 1. • Arm B: Leuprolide acetate 3-M depot injection, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China). Primary Endpoint • Sustained castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). Secondary Endpoints • Describe effects on serum testosterone: o Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4, prior to dosing on Week 3 Day 1; o Profound castration rate defined as the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) while on study treatment from Week 25 Day 1 through Week 49 Day 1; o Time to testosterone recovery in approximately 100 patients randomized to relugolix and approximately 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of leuprolide acetate 3-M depot); • Describe effects on PSA: o Proportion of patients with confirmed PSA response by Prostate Cancer Clinical Trials Working Group 3 guidelines at the Week 3 and Week 5 visits [Scher, 2016]; o Proportion of patients with PSA concentration < 0.2 ng/mL (0.2 µg/L) at the Week 25 visit; • Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable during the Follow-up and/or at End of Treatment visits; • Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as the EuroQol EQ-5D-5L questionnaire, at regular intervals during treatment, and as applicable during the Follow-up visits; • Incidence of adverse events; • Incidence of abnormalities in clinical laboratory data; • Endocrine marker effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for: o LH at the Day 4, Week 5, Week 25, and Week 49 visits; o FSH at the Day 4, Week 5, Week 25, and Week 49 visits; o Dihydrotestosterone at the Week 5, Week 25, and Week 49 visits; and o Sex hormone binding globulin at the Week 5, Week 25, and Week 49 visits; • Predose relugolix plasma concentrations;

	• Single and repeat-dose plasma relugolix PK parameters such as maximum plasma concentration (C_{max}), area under the concentration-time curve from time 0 to the end of the dosing interval ($AUC_{0-\tau}$), and time to maximum plasma concentration (t_{max}) in a subset of patients from China (if enrolled) and Japan during the Day 1 visit. • Time-to PSA progression; • Proportion of patients with confirmed PSA progression among those who have achieved sustained testosterone suppression during the 48-week treatment. <u>Exploratory Endpoints</u> • Overall survival defined as time from randomization to date of death prior to data cutoff date; and • The presence of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix. These will be evaluated in a subset of patients.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) population defined as all randomized patients who have taken at least one dose of study treatment. Randomization will be stratified by geographic region (North and South America versus Europe versus Asia and Rest of World), presence of metastatic disease on baseline imaging (yes versus no), and age (≤ 75 years old versus > 75 years old). The 2-sided type I error rate for this study is 0.05.

Primary Efficacy Endpoint:

The primary efficacy endpoint is the sustained castration rate defined as the cumulative probability of achieving testosterone suppression to castrate levels of ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). This probability will be estimated for each treatment group using the Kaplan-Meier method with the confidence interval calculated using the exponential Greenwood formula via log-log transformation of the survival function. Patients who discontinue treatment prior to observing a testosterone level > 50 ng/dL (1.7 nmol/L) will be censored at the last testosterone assessment prior to discontinuation. Detailed censoring rules will be prespecified in the statistical analysis plan.

There are 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit:

- Evaluation Criterion 1: to determine whether the sustained castration rate for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression to castrate levels in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion.
- Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot as assessed by the cumulative probability of sustained testosterone suppression to castrate levels. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression to castrate levels between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.

The 2-sided type I error rate will be 0.05 for each individual evaluation criterion.

Secondary Efficacy Endpoints:

1. Castration rate: the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4, and prior to dosing on Week 3 Day 1;
2. Profound castration rate: the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) from Week 25 through Week 49;
3. PSA response rate: proportion of patients with a ≥ 50% decrease in PSA from baseline at Week 3 and confirmed at Week 5;
4. Undetectable PSA rate: proportion of patients with PSA concentration < 0.2 ng/mL (0.2 µg/L) at the Week 25 visit;
5. Time to testosterone recovery in approximately 100 relugolix-treated and approximately 50 leuprolide acetate-treated patients who complete 48 weeks of treatment and do not start alternative androgen deprivation therapy within 12 weeks after the last dose of relugolix or within 24 weeks following the last received injection of leuprolide acetate. Kaplan-Meier methods will be used to describe survival distributions;
6. Quality of Life: absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-

treatment-related symptom subdomains, at regular intervals during treatment, and as applicable at the Follow-up and/or End-of-Study visits will be presented. Additionally, absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as EQ-5D-5L, at regular intervals during treatment, and as applicable during the Follow-up visits will be presented. Change from baseline will be analyzed using mixed-model repeated measures methodology;
7. Time to PSA progression;
8. Proportion of patients with confirmed PSA progression among those who have achieved sustained testosterone suppression during the 48-week treatment period.

Exploratory Endpoints:

1. Overall survival: Overall survival defined as time from randomization to date of death prior to data cutoff date. Kaplan-Meier methods will be used to describe survival distributions;
2. The effect of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or drug metabolizing enzymes and transporter proteins on the efficacy and safety of relugolix will be described in a separate statistical analysis plan.

The methods and procedures needed to maintain a study-wide 2-sided type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

Pharmacokinetics

Relugolix plasma concentrations will be summarized and described using population PK methods. Plasma PK parameters in a subset of patients from China (if enrolled) and Japan will be determined using noncompartmental methods.

Safety

Safety assessments, including adverse events, vital signs, clinical laboratory tests, and ECGs, will be summarized for the treatment-emergent period. The treatment-emergent period is defined as the time from first dose of study drug through 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last dose of leuprolide acetate. Safety analyses will be based on all randomized patients who receive any amount of study drug (Safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher-level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive rather than inferential statistics will be used. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of baseline versus post baseline results will be produced.

An independent Data and Safety Monitoring Board will monitor all available safety data on a periodic basis. The roles and responsibilities of the Data and Safety Monitoring Board will be described in detail in a separate charter.

Sample Size

To calculate the sample size required for the primary efficacy endpoint of this study, the following assumptions have been made:

- True probabilities of sustained castration rates are 94% and 96% for relugolix and leuprolide acetate, respectively;
- 2:1 randomization ratio (relugolix:leuprolide acetate);
- Dropout rate of 15%.

For Evaluation Criterion 1, 610 patients in the relugolix group will provide approximately 90% power to rule out a fixed probability of sustained testosterone suppression of ≤ 90% at a 2-sided type I error rate of 0.05.

For Evaluation Criterion 2, with the non-inferiority margin of -10% and a 2-sided type I error rate of 0.05, a total of approximately 915 patients (610 relugolix, 305 leuprolide acetate) will yield at least 99% power in declaring the non-inferiority of relugolix compared to leuprolide acetate.

The primary analysis of the primary efficacy endpoint will be performed after at least 915 patients have had the opportunity to complete 48 weeks of study drug treatment. The evaluation criteria used for the primary efficacy endpoint assessment will be determined by regional regulatory requirements and will be prespecified in separate regional statistical analysis plans.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3201

Period	**Screening Visit**	**Treatment Period Visits**													**Follow-up[a,c]**		
															Safety[b]	**Testosterone Recovery**	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2[q]**	**Wk 3**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17 and 21**	**Wk 25**	**Wk 29 and 33**	**Wk 37**	**Wk 41 and 45**	**Wk 49[e]**	**Un-scheduled**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**		**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**		**±2 days**			**± 7 days**										**± 7 days**		
Informed Consent[f]	X																	
Inclusion/ Exclusion Criteria	X	X																
Study Drug Dispensation: Relugolix		X				X	X	X	X	X	X	X	X		X[r]			
Study Drug Administration: Relugolix Once Daily		X	X Patients will receive a single loading dose of oral relugolix 360 mg on Day 1 in the clinic; Starting on Day 2, patients will take oral relugolix 120 mg once daily												X[r]			
Study Drug Administration: Leuprolide Acetate 3-M Depot		X						X		X		X			X[r]			
Phone call prior to visit and study drug accountability[d]						X	X	X	X	X	X	X	X	X	X[r]			
Demographics	X																	
Medical History (including detailed prostate cancer history)	X	X																

Period	Screening Visit	Treatment Period Visits														Follow-up[a,c]		
																Safety[b]	Testosterone Recovery	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2[q]**	**Wk 3**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17 and 21**	**Wk 25**	**Wk 29 and 33**	**Wk 37**	**Wk 41 and 45**	**Wk 49[e]**	**Un-scheduled**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**		**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**		**±2 days**			**± 7 days**										**± 7 days**		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X	X
Weight, BMI	X	X						X		X				X	X[r]	X		
Height	X														X[r]			
12-lead ECG[g]	X	X				X		X		X				X	X[r]	X		
ECOG Performance Assessment	X	X								X				X	X[r]	X		
Complete Physical Exam and Visual Acuity[h]	X									X				X	X[r]			
Symptom Based Physical Exam		X				X	X	X	X		X	X	X		X[r]	X	X	X
Abdominopelvic CT or MRI and Bone Scan[i]	X														X[r]			
EuroQol EQ-5D-5L Health Questionnaire		X				X		X		X		X		X	X[r]	X	X	X
EORTC-QLQ-PR25 and EORTC-QLQ-C30 Quality of Life Questionnaires		X				X		X		X		X		X	X[r]	X	X	X
Adverse Events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X	X
Hematology	X	X						X		X		X		X	X[r]	X		
Chemistry	X	X				X		X		X		X		X	X[r]	X		

Period	Screening Visit	Treatment Period Visits														Follow-up[a,c]		
																Safety[b]	Testosterone Recovery	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2[q]**	**Wk 3**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17 and 21**	**Wk 25**	**Wk 29 and 33**	**Wk 37**	**Wk 41 and 45**	**Wk 49[e]**	**Un-scheduled**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**		**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**		**±2 days**			**± 7 days**										**± 7 days**		
Lipid & HbA1c[k]	X									X				X	X[r]	X		
PSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X	X
Serum Testosterone	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[r]	X	X	X
LH/FSH		X	X			X				X				X	X[r]	X	X	X
SHBG/DHT		X				X				X				X	X[r]			X
Blood Sample for Relugolix PK[m,n]		X[m,n]	X[n]	X[n]		X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[r]			
Blood Sample for DNA[o]		X													X[r]			
Health Status Survey[p]														X	X[r]			

Abbreviations: 3-M, 3-month; BMI, body mass index; CT, computed tomography; DHT, dihydrotestosterone; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; EuroQol EQ-5D-5L, European Quality of Life 5-Dimension 5-Level; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; LH, luteinizing hormone; MRI, magnetic resonance imaging; PK, pharmacokinetics; PSA, prostate-specific antigen; SHBG, sex hormone binding globulin

a. The study day in which the Follow-up visit occurs is not specified in the table because these visits occur relative to when the patient takes his last dose of study drug. The End of Treatment (EOT) is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.
b. May occur earlier for patients who are starting alternative androgen deprivation therapy, or do not complete 12 weeks of study treatment. Adverse events, serious adverse events, and concomitant medications should continue to be collected and recorded through 30 days after the End of Treatment. All other study procedures should be completed before the start of alternative androgen deprivation therapy.
c. Patients who have started alternative androgen deprivation therapy will not participate in the 60- and 90-day Follow-up visits. For approximately 100 patients receiving relugolix and approximately 50 patients receiving leuprolide acetate who complete 48 weeks of study drug treatment and, in the opinion of the investigator, can remain off androgen deprivation therapy for 90 days will be included in the testosterone recovery 60- and 90-day Follow-up visits.
d. For patients assigned to the relugolix treatment arm, the patient should be called 7 days before their next visit to check on compliance with their study medication. Study drug accountability will be conducted at visits and results will be recorded as the primary source of study drug accountability.
e. If patient terminates early from study treatment, the patient should be asked to come in as soon as possible and complete this visit.
f. The informed consent form must be signed before any study-mandated procedures are performed.

g. 12-lead ECGs should be read locally by a qualified physician.
h. A complete physical examination should be performed. Visual acuity will be evaluated by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment. Patients whose presenting visual acuity score is 90 or lower at the screening visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, i.e., an ophthalmologist or an optometrist. Any findings (i.e., diagnoses) from the eye examination should be recorded as medical history. Patients whose presenting visual acuity score at Week 25, Week 49, or Early Termination has decreased by 10 or more points from the screening visit should be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor
i. An abdominopelvic CT or MRI and a bone scan should be performed and read locally to determine the presence of metastatic disease within 60 days prior to randomization. However, if CT or MRI demonstrates presence of metastatic disease, a bone scan is not required. If metastatic disease is not present on CT or MRI, then a bone scan is also required.
j. Collect serious adverse event information from the time of signed informed consent through the Safety Follow-up Visit, which is through 30 days after the last dose of relugolix or 12 weeks and 30 days after the last injection of leuprolide acetate, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit (or from the time of signed informed consent if event was related to a screening study procedure through approximately 30 days after the last dose of relugolix or 12 weeks and 30 days after the last injection of leuprolide acetate, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first.
k. Blood samples must be obtained fasting; nothing to eat or drink (other than water) for at least 9 hours prior to obtaining the sample.
l. All testosterone samples obtained from Week 5 and beyond are to be collected during a ± 7-day window.
m. Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose, approximately 24 hours after the previous dose. Patients may be dosed in the clinic at these visits, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing.
n. A subset of patients from China (if enrolled) and Japan will have additional samples collected predose, and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Day 1 and Week 2 visits. Patients will be dosed in the clinic at these visits. The dose will be administered at least 2 hours after food; food should be withheld for 1 hour after dosing. A predose sample (approximately 24 hours after the previous dose) also will be collected at the Day 4 visit. Patients may be dosed in the clinic at the Day 4 visit, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing.
o. The blood sample for DNA should be collected at the Baseline Day 1 visit, but may be collected at any visit if it is missed at that visit.
p. During the final weeks prior to database lock, sites will be asked to contact all study participants or their immediate family regarding the current health status of previously enrolled/completed study patients.
q. Week 2 visit will only occur for patients who are part of the Japan or China subset for PK analysis.
r. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.

2. INTRODUCTION

2.1. Prostate Cancer

Prostate cancer is the most prevalent form of cancer in men and the second leading cause of death due to cancer in men in the US [Greenlee, 2001] and Europe [Ferlay, 2007]. The median age of diagnosis is 70 years, and diagnosis before the age of 40 years is rare [Cersosimo, 1996]. In Japanese men, prostate cancer was the fourth leading cancer diagnosis in 2007 [Foundation for Promotion of Cancer Research, 2012]. The incidence of invasive prostate cancer increases with age; a clear increase is seen among men aged 60 years or older [Siegel, 2014].

If prostate cancer is diagnosed at a stage where it is confined to the prostate gland and immediate surroundings, it is generally treated by surgical removal of the prostate gland, or prostatectomy, or with radiation. Often, these procedures are successful in curing men of their disease. Men whose disease progresses after prostatectomy or radiation are said to have advanced prostate cancer. Advanced prostate cancer is defined as either: PSA biochemical relapse following primary surgical or radiation therapy of curative intent; newly diagnosed metastatic prostate cancer; or advanced localized disease for which immediate radiation or surgical therapy is not indicated. The cure rate following surgery, depending on the stage of the cancer, is about 70% overall and, following radiation, about 50% to 60%.

Approximately 25% to 30% of men will, therefore, progress to advanced disease, excluding those with metastatic disease at the time of diagnosis. Androgens, such as testosterone and its more potent metabolite dihydrotestosterone, are strong tumor promoters for prostate cancer [Bosland, 2014]. Through the androgen receptor, they synergistically augment the effect of other tumor promoters or carcinogens. Although prostate cancer is driven by presumed mutations in other tumor promoting pathways and/or by translocations leading to aberrant activation of the androgen receptor pathway, most early-stage prostate cancer cells remain either sensitive to or dependent upon circulating androgens. Thus, for more than 60 years, androgen deprivation therapy with surgical or medical castration has been the foundational therapy for either advanced inoperable or metastatic cancer. Increasingly, androgen deprivation therapy is used earlier as a neoadjuvant/adjuvant treatment to radiation therapy or for biochemical or clinical relapse after local therapies of curative or palliative intent. More than 80% of men with progressive or advanced disease initially respond to androgen deprivation therapy with varying degrees of tumor regression or stabilization [Kreis, 1995]. The duration and depth of response to androgen deprivation therapy is presumably dependent on the underlying tumor biology and burden. Thus, patients with metastases respond for an average of 2 years before any biochemical evidence of castration resistance occurs. By contrast, patients with biochemical-only evidence of progressive disease may respond to androgen deprivation therapy for 5 years or more [Klotz, 2015].

Currently, most patients in developed countries receive medical rather than surgical castration. GnRH (or LH-releasing hormone) agonists (ie, long-acting leuprolide acetate depot injections) are the current mainstay of medical castration, causing long-term desensitization and down regulation of the hypothalamic-pituitary gonadal axis. One disadvantage of the agonist form of GnRH is the initial stimulation of the axis lasting 1 to 3 weeks that occurs prior to desensitization. This results in a rise in LH and testosterone levels and an increase in clinical symptoms. In addition, at the time of repeat injection of GnRH agonist depot, microsurges of

LH and testosterone may occur, although the apparent incidence is low [Klotz, 2008]. The initial flare response may be managed with simultaneous antiandrogen administration, such as with bicalutamide.

Recently, GnRH antagonists, in particular degarelix, [Firmagon, 2016], have become available as an alternative form of medical castration. Degarelix, an injectable peptide, has been approved in some countries for the treatment of patients with advanced prostate cancer. As a GnRH antagonist, degarelix achieves medical castration and PSA response with no initial agonist activity within the first 1 to 2 weeks of administration, and effectively can obviate the need for concomitant antiandrogen treatment. Post-hoc analyses of degarelix trials [Tombal, 2010] suggest that it may have additional advantages regarding disease response or secondary relapse; however, such differences require confirmation in prospective studies. Because of the need for monthly depot injections, with large volumes and accompanying local reactions, the use of degarelix in clinical practice has remained low.

Relugolix, previously known as TAK-385, is a potent and highly selective oral small molecule antagonist for the human GnRH receptor. For patients, relugolix may offer the advantages conferred by a direct receptor antagonist, including a more rapid onset of action and the absence of clinical flare or worsening of symptoms from the initial rise in androgens caused by GnRH agonists, as well as having the added convenience and relative comfort of oral dosing.

2.2. Relugolix

2.2.1. Indication

Relugolix is being developed as a once daily oral medication for the treatment of advanced prostate cancer. The proposed dose of relugolix is 120 mg administered orally once daily following a loading dose of 360 mg (three 120-mg tablets) on Day 1.

2.2.2. Pharmacology

Relugolix is an orally-active, potent, highly-selective, high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes the human GnRH receptors present on the gonadotrophin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in testosterone in men and estradiol and progesterone levels in women. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 µg·hr/mL, which is ~51 times higher than the estimated exposure (area under the concentration-time curve [AUC]) in men receiving 120 mg once daily (0.469 µg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 µg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥ 100 mg/kg (estimated C_{max} of 4.0 µg/mL), but did not prolong the QT interval in a human Thorough QT study at doses up to 360 mg (C_{max} of 0.181 µg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and 3 phase 2 studies have been completed. In addition, 6 clinical studies evaluating relugolix are ongoing, including 2 phase 1 studies, 2 phase 2 studies in men with prostate cancer (US and Europe), and 2 phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least one dose of relugolix, including 158 women receiving relugolix 40 mg once daily for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of testosterone in male subjects and estradiol in female subjects. After oral

administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The PK and pharmacodynamics of relugolix have been evaluated, and appear to be similar in Western and Asian volunteers, despite the lower mean body mass index observed in Asian volunteers.

A relative bioavailability and food effect study was conducted using the global phase 3 prostate cancer formulation of 120 mg relugolix. After administration with a high-fat, high-calorie breakfast, the C_{max} and AUC of relugolix were reduced, on average, by 21.4% and 18.8%, respectively.

In the phase 1 study C27001, serum LH, FSH, dihydrotestosterone, and testosterone concentrations were determined in healthy men following single and multiple oral doses of relugolix or placebo for up to 28 days. Loading doses of ≥ 160 mg on Day 1 were used to shorten the time to testosterone suppression. Relugolix caused an immediate and effective suppression of LH, FSH, and testosterone. After 14 days of once daily dosing, mean LH and serum testosterone concentration profiles were similar for the 40, 80, and 180 mg relugolix dose cohorts. LH, FSH, and testosterone concentrations began decreasing 2 to 6 hours postdose on Day 1 and remained suppressed through Day 14. However, the relugolix once daily maintenance dose was a major determinant of sustained testosterone suppression. Profound castration (defined as average testosterone levels < 20 ng/dL or 0.7 nmol/L) was achieved with 40, 80, or 180 mg once daily for 14 days; however, 20 mg once daily was insufficient in maintaining adequate suppression of serum LH and testosterone concentration levels during the second week.

In healthy, older men receiving 14 or 28 days of dosing, effective castration was consistently achieved over 14 and 28 days dosing at daily doses of 40 to 180 mg (14 days) and 80 to 160 mg (28 days). Use of a loading dose for up to 3 days (or once daily doses of ≥ 160 mg) resulted in castration levels of testosterone (< 50 ng/dL or 1.7 nmol/L) within 24 to 48 hours. Results obtained after 28 days of dosing suggested that the likely minimal, fully effective maintenance dose for sustained castration would be relugolix ≥ 80 mg once daily. Doses of 80 mg and 120 mg were moved forward into phase 2 development.

Relugolix is to be administered in the fasted state (at least 1 hour before or 2 hours after a meal), as food decreases the extent of relugolix absorption by approximately 20%. The exposure of relugolix is increased by inhibitors of P-glycoprotein up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 (CYP) 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong QTc at single doses of 60 or 360 mg.

2.2.4.2. Clinical Studies in Men with Prostate Cancer

One phase 1 study and 2 phase 2 studies have been conducted evaluating relugolix in men with prostate cancer.

Study TB-AK160108 is an ongoing multicenter phase 1, open-label, dose range-finding study conducted in hormone treatment-naïve Asian patients with non-metastatic prostate cancer. The study consists of a dose-rising phase (Part A) and an expansion phase (Part B). In Part A, a loading dose of relugolix (320 or 360 mg) was administered on Day 1 followed by once daily dosing on Days 2 through 28, with the dosage dependent on the individual cohort of 3 to 4

patients each. In Part B, 30 patients receive a maximum of 96 weeks treatment at doses of 80 and 120 mg once daily (N = 15 each arm, loading dose of 320 mg on Day 1). Testosterone reduction by both doses of relugolix was rapid and sustained through 48 weeks. Both the 80- and 120-mg once daily doses were evaluated in phase 2 clinical studies.

Study C27003 is a phase 2 study that enrolled men in North America or the United Kingdom requiring 6 months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily following a single oral loading dose of 320 mg (N = 65) or to degarelix 80 mg subcutaneously every 4 weeks following a single loading dose of 240 mg (N = 38) for 24 weeks. External beam radiation therapy was initiated for most patients between Week 13 and Week 15.

Relugolix 120 mg administered orally once daily rapidly suppressed testosterone levels below the castration threshold (50 ng/dL [1.7 nmol/L]) within the first week of therapy and maintained those levels from the end of Week 4 through at least 24 weeks. The levels of testosterone suppression achieved by relugolix were similar to those achieved by monthly injections of degarelix. Profound castration rates below the lower testosterone threshold of < 20 ng/dL (0.7 nmol/L) were also similar in the relugolix and degarelix groups (Table 2-1).

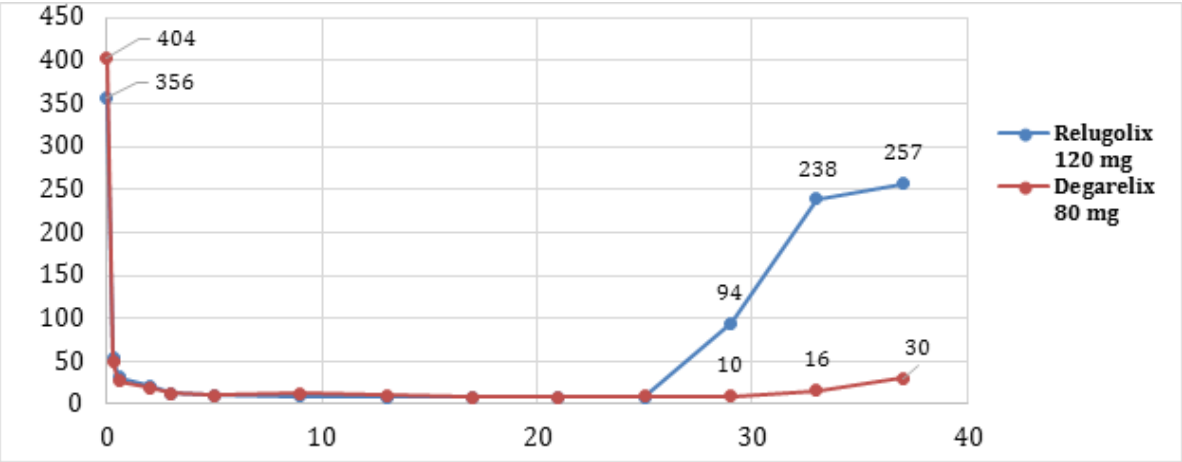
Table 2-1 Study C27003: Sustained Castration Rates (Percentage of Men Achieving Testosterone Suppression to < 50 ng/dL [1.7 nmol/L]) through 24 Weeks

	Relugolix 120 mg QD[a] N = 65	**Degarelix 80 mg Q4W[b] N = 38**
Castration rate over 24 weeks, % (95% CI)	95% (87.1, 99.0)	89% (75.2, 97.1)

Note: Castration rate is defined as the estimated proportion of patients who have testosterone concentrations < 50 ng/dL at all scheduled visits Week 5, Day 1 to specific time point (Week 25, Day 1).
Abbreviations: CI, confidence interval; Q4W, once every 4 weeks; QD, once daily
a. Loading dose of 320 mg on Day 1
b. Loading dose of 240 mg on Day 1, then dosed every month

The percentage PSA reductions and absolute PSA values over time were consistent with the rapid testosterone reductions observed with both therapies and were similar between the relugolix and degarelix treatment arms. Prostate gland size was measured during screening and following 8 to12 weeks of study drug treatment. In both treatment groups, the average reduction in estimated prostate volumes was similar, approximately 30%. Following discontinuation of therapy at the end of 24 weeks, patients were followed for an additional 12 weeks to evaluate testosterone recovery and associated changes in PSA and quality of life. At the end of the follow-up period, approximately half of the patients receiving relugolix had recovered either to the baseline testosterone value or to > 280 ng/dL, whichever was less, compared to only 6% of patients receiving degarelix (Figure 2-1).

Figure 2-1 Study C27003: Testosterone Recovery Following Discontinuation of Relugolix and Degarelix at Week 25



Note: Y-axis shows testosterone value (ng/dL); x-axis shows study week.

Study C27002 is a phase 2 study of relugolix and leuprolide acetate in patients with prostate cancer who require first-line androgen deprivation therapy, which is ongoing in North America. This study was designed to help plan the population, dosing, and assessment schedules for phase 3 studies in patients with advanced prostate cancer. Eligible patients in C27002 have evidence of advanced prostate cancer including either: 1) PSA biochemical relapse following primary surgical or radiation therapy of curative intent; 2) newly diagnosed metastatic prostate cancer; or 3) advanced localized disease for which immediate radiation or surgical therapy is not indicated. In this open-label, parallel group study, patients were randomized to receive 1 of 2 dose levels of oral relugolix (80 or 120 mg [patients randomized to relugolix received a loading dose of 320 mg on Day 1], N = 50 per group) or to an observation cohort to receive standard GnRH therapy with leuprolide acetate 22.5 mg administered by intramuscular injection every 12 weeks (N = 25). Relugolix or leuprolide acetate was administered for up to 48 weeks with patients randomized to leuprolide acetate receiving their last on-study 12-week depot injection at Week 37.

The primary objective of this phase 2 study was to evaluate the ability of relugolix to achieve and maintain testosterone suppression (< 50 ng/dL [1.7 nmol/L]) through Week 25. Results from the completed study C27002 demonstrate that both doses of relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold within the first week of therapy and maintained those levels in 91% of patients through 24 weeks of treatment (Table 2-2).

Table 2-2 Study C27002: Castration Rates (Percentage of Men Achieving Testosterone Suppression to < 50 ng/dL [1.7 nmol/L] through 24 Weeks)

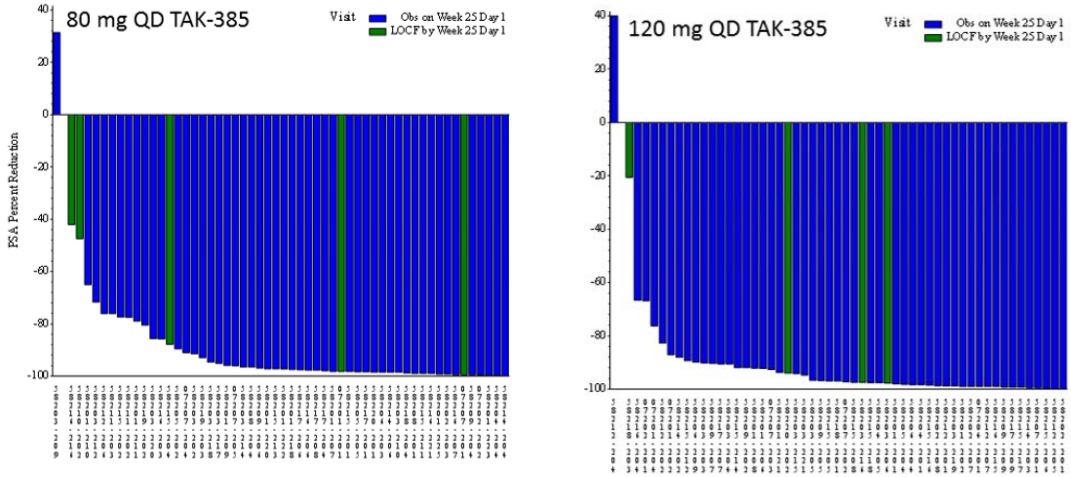
	Relugolix			Leuprolide Acetate 22.5 mg Q12W N = 24
	80 mg QD N = 56	120 mg QD N = 54	Total N = 110	
Patients with at least 1 dose of treatment, n	56	54	110	24
Castration rate[a] over 24 weeks				
n (%)	51 (91)	49 (91)	100 (91)	23 (96)
95% CI[b]	80.4-97.0	79.7-96.9	83.9-95.6	78.9-99.9
Profound castration rate[c] over 24 weeks				
n (%)	39 (70)	41 (76)	80 (73)	18 (75)
95% CI[b]	55.9-81.2	62.4-86.5	63.4-80.8	53.3-90.2

Abbreviations: CI, confidence interval; Q12W, once every 12 weeks; QD, daily

a. Castration rate was defined as the estimated proportion of patients who have testosterone concentrations < 50 ng/dL at all scheduled visits Week 5 Day 1 to specific time point.
b. The 2-sided 95% CI was calculated using the normal approximation method, if the number of non-castration patients was = 5 in any treatment arm, the exact CI was presented.
c. Profound castration rate was defined as the estimated proportion of patients who had testosterone concentrations < 20 ng/dL at all scheduled visits Week 13 Day 1 through specific time point.

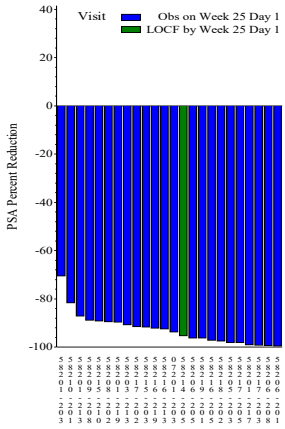
Castration to below the lower testosterone threshold of < 20 ng/dL was also similar in the 2 relugolix arms and to that observed in the leuprolide acetate arm. On average, in patients receiving relugolix, testosterone decreased to below the castration threshold of 50 ng/dL (1.7 nmol/L) by the Day 4 visit, and to below the profound castration threshold of 20 ng/dL (0.7 nmol/L) by the Week 5 visit. In contrast, in patients receiving leuprolide acetate, testosterone levels rose during the first 1 to 2 weeks of therapy and then declined to castrate levels by Week 5. PSA responses between the 2 relugolix arms and leuprolide acetate were similar as demonstrated by PSA waterfall plots showing the reduction in PSA from baseline for individual patients (Figure 2-2 [relugolix] and Figure 2-3 [leuprolide acetate]).

Figure 2-2 Study C27002: Waterfall Plots of Prostate-Specific Antigen Percent Reduction by Dose of Relugolix at Week 25 Day 1



Note: Last observation carried forward method was used to impute percent prostate-specific antigen reductions for patients without an observation at Week 25 Day 1.
Abbreviations: LOCF, last observation carried forward; Obs, observed; PSA, prostate-specific antigen; QD, once daily; TAK-385, relugolix

Figure 2-3 Study C27002: Waterfall Plot of Prostate-Specific Antigen Percent Reduction by Leuprolide Acetate at Week 25 Day 1



Notes:
The leuprolide acetate dose was 22.5 mg every 12 weeks.
Last observation carried forward method was used to impute percent prostate-specific antigen reductions for patients without an observation at Week 25 Day 1.
Abbreviations: LOCF, last observation carried forward; Obs, observed; PSA, prostate-specific antigen

A more detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix

Investigator Brochure, Version 9.0, dated 09 November 2016, along with a full discussion of the safety profile of relugolix.

2.2.4.3. Clinical Safety of Relugolix in Men with Prostate Cancer

A full description of the safety data for relugolix from clinical trials is available in the Investigator Brochure. Overall, approximately 632 healthy volunteers (330 women, 302 men), 535 female patients with uterine fibroids (N = 229) or endometriosis (N = 306), and 218 male patients with prostate cancer received at least 1 dose of relugolix. Data from the 175 patients with prostate cancer who received relugolix in randomized, open-label, parallel-group phase 2 studies, C27002 and C27003, provide the basis for the frequency of expected adverse events associated with relugolix in the prostate cancer indication. The adverse drug reactions in the prostate cancer indication observed in the phase 2 studies include hot flush (59%), fatigue (26%), arthralgia (10%), nausea (5%), and gynecomastia (3%). No clinical evidence of PLD has observed in any relugolix clinical study.

Leuprolide Acetate 3-Month Depot

Leuprolide acetate depot is indicated for the palliative treatment of advanced prostatic cancer.

Leuprolide acetate acts as an agonist at pituitary GnRH (gonadotropin-releasing hormone) receptors. Leuprolide acetate has greater receptor affinity, reduced susceptibility to enzymatic degradation, and is approximately 100-fold more potent than the natural GnRH molecule. GnRH agonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, causing an initial release of both LH and FSH, which causes a subsequent increase in testosterone production from testicular Leydig cells. Initially, leuprolide acetate stimulates LH production, which in turn causes a surge of testosterone and dihydrotestosterone for 5 to 12 days before the ultimate inhibition of LH. This androgen surge of male hormones can cause a flare reaction ("clinical flare"), which may lead to an increase in bone pain, bladder obstruction, or other symptoms due to prostate cancer [Tolis, 1982; Schally, 1980; Waxman, 1985; Conn, 1991; Limonata, 2001].

Chronic stimulation by the GnRH agonist ultimately desensitizes the GnRH receptors, downregulating the secretion of gonadotropins, LH, and FSH, leading to hypogonadism and thus a dramatic reduction in testosterone and dihydrotestosterone, on which continued growth of prostate cancer cells depends. The fall in serum LH leads to a decrease in serum testosterone to castrate levels within 3 to 4 weeks after the start of treatment. Continued treatment maintains serum testosterone at castrate levels.

The decrease in testosterone production is generally reversible over time upon cessation of GnRH agonist therapy. However, testosterone production does not always return to baseline levels and may be related to the duration of GnRH agonist therapy, patient age, and other factors.

The flare phenomenon can be effectively prevented with antiandrogen therapy, which blocks the effect of the increased serum testosterone [Loblaw, 2004]. First generation antiandrogens such as flutamide, bicalutamide, and nilutamide bind to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone. They are often used in an attempt to limit the clinical sequelae produced by the hormonal surge resulting from GnRH agonist treatment.

The most common adverse reactions (> 10%) reported for marketed formulations of leuprolide acetate depot in common use include the following examples:

- Leuprolide (leuprorelin) acetate 11.25 mg: weight fluctuation, hot flash, hyperhidrosis, muscle weakness, bone pain, decreased libido, erectile dysfunction, testicular atrophy, fatigue, injection site reaction [Prostap 3 DCS, 2016]
- Leuprolide acetate 22.5 mg: hot flashes, ecchymoses, erythema, fatigue, injection site burning, injection site paraesthesia [Eligard, 2017]

In post marketing experience, mood swings, depression, rare reports of suicidal ideation and attempt, rare reports of pituitary apoplexy have been reported. Leuprolide has been associated with mild liver enzyme elevations (generally transient and asymptomatic) during therapy in 3-5% of patients; values above 3 times the upper limit of normal are rare, being reported in less than 1% of recipients. A risk of developing or worsening diabetes has been reported in men receiving this class of drug.

The package insert (approved labeling) for the leuprolide acetate study drug provided for this study should be referenced for warnings, precautions, and safety information.

3. STUDY OBJECTIVES AND ENDPOINTS

This phase 3 trial has 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit as listed briefly below and described in detail in the statistical analysis plan. Patients enrolled into this phase 3 trial will be randomized 2:1 to either relugolix 120 mg once daily following an oral loading dose of 360 mg on Day 1, or to leuprolide acetate 22.5 mg (or 11.25 mg Japan, Taiwan, and China) 3-M depot injection. Patients randomized to leuprolide acetate will also receive an antiandrogen if indicated at the discretion of the investigator.

The first criterion for the primary efficacy endpoint will evaluate only patients randomized to relugolix. The second criterion for the primary efficacy endpoint will evaluate the non-inferiority of patients randomized to relugolix to those randomized to leuprolide acetate as described below.

Objectives	Endpoints
Primary	
• To evaluate the ability of relugolix to achieve and maintain serum testosterone suppressed to castrate levels of ≤ 50 ng/dL (1.7 nmol/L) in patients with androgen-sensitive advanced prostate cancer.	The primary endpoint is the sustained castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). • Evaluation Criterion 1: to determine whether the sustained castration rate (defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL [1.7 nmol/L] while on study treatment from Week 5 Day 1 through Week 49 Day 7) for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be at least 90% to meet this criterion. • Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot injection as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.
Secondary	
• To evaluate the time course and change in serum testosterone during treatment with relugolix;	• Describe effects on serum testosterone: o Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4 and prior to dosing on Week 3 Day 1; o Profound castration rate defined as the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) while on treatment from Week 25 Day 1 through Week 49 Day 1);

Objectives	Endpoints
• To evaluate the time course and magnitude of PSA reduction during treatment with relugolix;	• Describe effects on PSA: o Proportion of patients with confirmed PSA response (by Prostate Cancer Clinical Trials Working Group 3 [Scher, 2016]) at the Week 3 and Week 5 visits; o Proportion of patients with PSA concentration < 0.2 ng/mL [0.2 µg/L] at the Week 25 visit;
• To evaluate testosterone recovery following discontinuation of relugolix;	• Time to testosterone recovery in approximately 100 patients randomized to relugolix and approximately 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of leuprolide acetate 3-M depot);
• To evaluate quality of life using validated patient-reported outcome instruments;	• Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable during the Follow-up and/or End of Treatment visits; • Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as the EuroQol EQ-5D-5L questionnaire, at regular intervals during treatment, and as applicable during the Follow-up visits;
• To evaluate the safety of relugolix 120 mg once daily in men with androgen-sensitive advanced prostate cancer;	• Incidence of adverse events; • Incidence of abnormalities in clinical laboratory data;
• To evaluate the effect of relugolix and leuprolide acetate on endocrine pharmacodynamic parameters;	• Endocrine marker effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for: o LH at the Day 4, Week 5, Week 25, and Week 49 visits; o FSH at the Day 4, Week 5, Week 25, and Week 49 visits; o Dihydrotestosterone at the Week 5, Week 25, and Week 49 visits; o Sex hormone binding globulin at the Week 5, Week 25, and Week 49 visits;

Objectives	Endpoints
• To collect relugolix plasma concentration data to further evaluate relugolix population PK and the relationship between relugolix exposure and serum testosterone; and	• Predose relugolix plasma concentrations;
• To characterize the relugolix plasma PK parameters in a subset of patients from China (if enrolled) and Japan;	• Single and repeat-dose plasma relugolix PK parameters such as C_{max}, $AUC_{0-\tau}$, and t_{max}.
• To describe the time course and magnitude of PSA progression and development of castration resistant prostate cancer during treatment with relugolix;	• Time to PSA progression • Proportion of patients with confirmed PSA progression among those who have achieved sustained testosterone suppression during the 48-week treatment
Exploratory	
• To explore the overall survival of patients treated with relugolix; and	• Overall survival defined as time from randomization to date of death prior to data cutoff date;
• To explore the contribution of genetic variance on drug response.	• The presence of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The HERO study is a phase 3 multinational randomized, open-label, parallel-group study to evaluate the safety and efficacy of relugolix in patients with androgen-sensitive advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy. Relugolix is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist that lowers testosterone by inhibiting pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Relugolix 120 mg orally once daily or leuprolide acetate depot suspension 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) every 3-months (3-M) will be administered to patients with prostate cancer who require androgen deprivation therapy. This study will evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) for 48 weeks in patients with androgen-sensitive advanced prostate cancer.

To be eligible for the study, a patient must be, in the opinion of the investigator, a candidate for at least 1 year of continuous androgen deprivation therapy for the management of androgen-

sensitive advanced prostate cancer and must not be a candidate for surgical therapy. Eligible patients include those with evidence of biochemical relapse (rising PSA) following local primary intervention with curative intent, newly diagnosed metastatic disease (excluding metastases to the brain), and/or advanced localized disease. Patients may receive radiotherapy, cryotherapy or high frequency ultrasound no sooner than 2 months after initiation of androgen deprivation therapy. Patients may be included if they have not previously received androgen deprivation therapy for more than 18 months, and if the androgen deprivation therapy was completed at least 3 months prior to baseline. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy. Baseline serum testosterone must be ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L) to be enrolled.

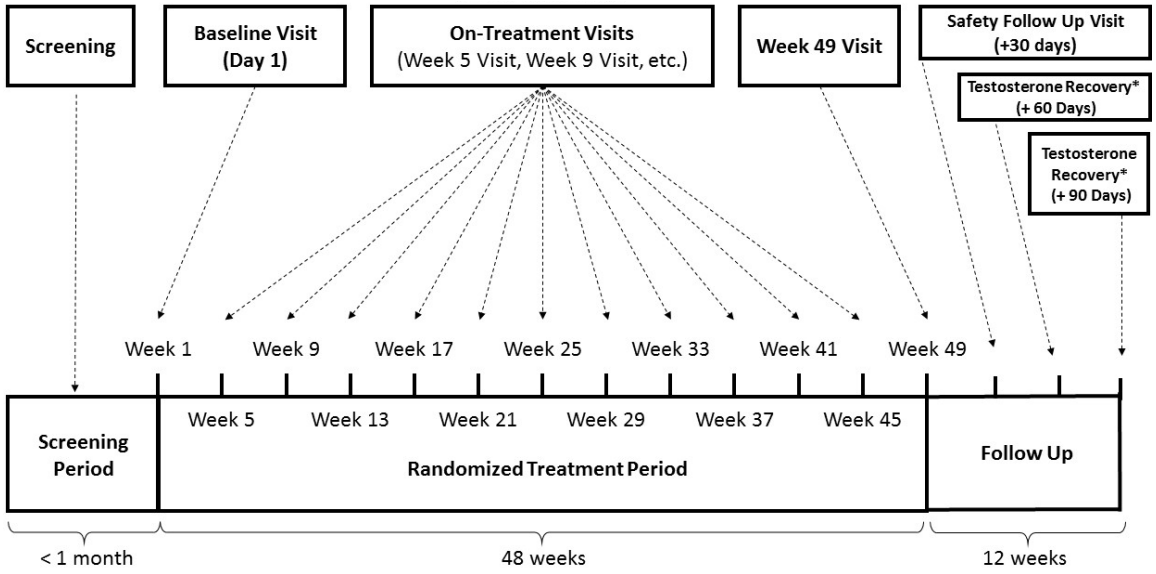
Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg once daily following a loading dose of 360 mg on Day 1 or 3-M depot of leuprolide acetate 22.5 mg (or 11.25 mg in Japan, Taiwan, and China). After randomization, patients on the leuprolide acetate arm may receive an antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator. Randomization will be stratified by geographic region, presence of metastatic disease, and age.

Approximately 915 patients will be enrolled in this study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region. The study includes a Screening Period of up to 28 days, a Treatment Period of 48 weeks, and a Follow-up Period of up to 90 days. Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed. Eligible patients will receive study treatment for 48 weeks. During that time, testosterone and PSA will be assessed monthly and patient-reported outcomes (EORTC-QLQ-C30, EORTC-QLQ-PR25, EuroQol EQ-5D-5L) will be assessed approximately every 3 months during the Treatment Period and more frequently during the Follow-up Period. Additional serum endocrine evaluations will include: LH, FSH, dihydrotestosterone, and sex hormone binding globulin. Relugolix PK samples will be collected throughout the study. Full PK profiles will be determined in a subset of patients in China (if enrolled) and Japan. Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead ECG, and visual acuity tests.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (testosterone level ≤ 50 ng/dL [1.7 nmol/L]), should remain on study and may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide. For patients requiring other systemic antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.

A schematic of the overall study design is provided in Figure 4-1.

Figure 4-1 Schematic of Study Design



Relugolix dosed daily (Baseline Day 1 – Week 48 Day 7)
Leuprolide Acetate dosed every 12 weeks (Baseline Day 1, Week 13 Day 1, Week 25 Day 1, and Week 37 Day 1)
*+60 Days and +90 Days Testosterone Recovery visits in subset of patients

4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is designed to establish the safety and efficacy of relugolix 120 mg orally once daily in men with advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy for androgen-sensitive disease. This study will focus on the primary objective of evaluating the ability of relugolix to achieve and maintain suppression of serum testosterone to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) in patients with advanced prostate cancer. During the Treatment Period of the study (Day 1 to Week 49 [Study Day 337]), patients will be randomized to one of the study treatment arms: oral loading dose of relugolix (360 mg) followed by 120 mg once daily of relugolix or leuprolide acetate 3-M depot injection of 22.5 mg (or 11.25 mg Japan, Taiwan, and China) at 12-week intervals for 48 weeks. Patients treated with leuprolide acetate will also receive an antiandrogen for 4 weeks or longer if indicated in the opinion of the investigator.

The study is designed to allow for global approvals, however, different regulatory agencies require different criteria for the demonstration of efficacy. The United States (US) Food and Drug Administration (FDA) requires, for approval, a primary efficacy criterion to determine whether the sustained castration rate (defined as the cumulative probability of testosterone ≤ 50 ng/dL [1.7 nmol/L] while on relugolix study treatment from Week 5 Day 1 through Week 49 Day 1) is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion. The study includes a leuprolide acetate arm to meet the regulatory requirement of other regions to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot injection as

assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.

The dose of relugolix selected is based on data from phase 1 and 2 studies demonstrating that oral doses of 80 mg and 120 mg once daily following an oral loading dose of 320 mg were able to suppress testosterone to castrate levels (see Section 2.2.4.2 and the Investigator Brochure). A loading dose of 360 mg (three 120-mg tablets) was selected for phase 3 so that only one tablet size was required. Leuprolide acetate 3-M depot injection was selected as the comparator as this is the GnRH agonist used most commonly as standard of care in the population under evaluation. Degarelix, an injectable GnRH antagonist, was considered, but was not used as it has limited market uptake attributed at least in part to a significant number of injection site reactions.

4.3. Selection of Study Population

Approximately 915 men with advanced prostate cancer requiring androgen deprivation therapy will be enrolled in this study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region. Enrollment is defined as the time at which a patient is randomized to a treatment group and receives at least one dose of study drug.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor prior to randomizing the patient.

4.3.1. Inclusion Criteria

A patient will be eligible for inclusion in this study only if all of the following inclusion criteria are met prior to randomization, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a male aged 18 years or older on the day of signing and dating the informed consent form;
3. Has histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate;
4. Is a candidate for, in the opinion of the investigator, at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer with one of the following clinical disease state presentations:
    a. Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, such as surgery, radiation therapy, cryotherapy, or high-frequency ultrasound and not a candidate for salvage treatment by surgery; or
    b. Newly diagnosed androgen-sensitive metastatic disease; or
    c. Advanced localized disease unlikely to be cured by local primary intervention with either surgery or radiation with curative intent;

Note: radiotherapy, cryotherapy, or high frequency ultrasound are allowed after 2 months of androgen deprivation therapy.

5. Has a serum testosterone at the Screening visit of ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L);
6. Has a serum PSA concentration at the Screening visit of > 2.0 ng/mL (2.0 µg/L), or, when applicable, post radical prostatectomy of > 0.2 ng/mL (0.2 µg/L) or post radiotherapy, cryotherapy, or high frequency ultrasound > 2.0 ng/mL (2.0 µg/L) above the post interventional nadir;
7. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at initial screening and at baseline (refer to Appendix 1);
8. Is a male patient who, even if surgically sterilized (ie, status post vasectomy):
    a. Agrees to use a male condom if having sex with a woman of childbearing potential or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or
    b. Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception;
9. Must agree not to donate sperm from first dose of study drug through 4 months after the last dose of study drug;
10. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

4.3.2. Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

1. In the investigator's opinion, is likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating androgen deprivation therapy;
2. Previously received GnRH analog or other form of androgen deprivation therapy (estrogen or antiandrogen) for > 18 months total duration. If androgen deprivation therapy was received for ≤ 18 months total duration, then that therapy must have been completed at least 3 months prior to baseline. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot;
3. Previous systemic cytotoxic treatment for prostate cancer (e.g. taxane-based regimen);
4. Metastases to brain per prior clinical evaluation;
5. *Removed*;
6. Scheduled for major surgery after baseline;
7. History of surgical castration;

8. Active malignancy beyond prostate cancer ***with the exception*** of any of the following:
   - Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ carcinoma of any type
   - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for ≥ 2 years
   - Any other cancer from which the subject has been disease-free for ≥ 5 years

   The medical monitor should be contacted for any questions regarding this exclusion criterion.
9. Abnormal laboratory values at the Screening visit that suggest a clinically unstable underlying disease, or the following laboratory values:
   a. Serum gamma-glutamyl transferase > 2.0 x ULN;
   b. Serum ALT and/or AST > ULN;
   c. Total bilirubin > ULN (unless secondary to Gilbert's syndrome or the pattern is consistent with a diagnosis of Gilbert's syndrome) or;
   d. Serum creatinine > 2.0 mg/dL (176.8 µmol/L);
   e. Platelets < 100 x 10^3/µL or history of bleeding disorder;
   f. Hemoglobin < 10.0 g**/**dL (100 g/L);
   g. Leukocytes (WBC) < 3 x 10^3/µL (3 GI/L);
   h. Absolute neutrophil count < 1.5 x 10^3/µL (1.5 GI/L);
10. Hemoglobin A1c (HbA1c) > 10% in patients previously diagnosed with diabetes mellitus. HbA1c > 8% in patients whose diabetes mellitus is previously undiagnosed. (Excluded patients may be rescreened after referral and evidence of improved control of their condition);
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (hepatitis A virus IgM positive), hepatitis B (HBsAg positive), or hepatitis C (HCV antibody positive, confirmed by HCV ribonucleic acid);
12. Known human immunodeficiency virus infection;
13. Any of the following within 6 months before Baseline Day 1:
    a. Myocardial infarction;
    b. Unstable angina;
    c. Unstable symptomatic ischemic heart disease;
    d. New York Heart Association (NYHA) class III or IV heart failure
    e. Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events);
    f. Any other significant cardiac condition (e.g., pericardial effusion, restrictive cardiomyopathy, severe untreated valvular stenosis, or severe congenital heart disease);
14. The following ECG abnormalities are excluded:

a. ECG evidence of acute ischemia;

b. Q-wave infarction, unless identified 6 or more months before the Screening visit;

c. QTc > 470 msec, measured by Fridericia's formula [QTcF = QT/(RR^0.33)]. If the QTc is prolonged in a patient with a pacemaker, the patient may be enrolled in the study if confirmed by the medical monitor;

d. Congenital long QT syndrome;

e. Active conduction system abnormalities. Examples of active conduction system abnormalities include the following:

- Mobitz II second degree heart block without a permanent pacemaker in place;
- Third degree heart block without permanent pacemaker in place;
- Untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
- Clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes;
- Uncontrolled atrial fibrillation (patients with chronic stable atrial fibrillation on stable anticoagulant therapy or patients with stable cardiac rhythm controlled by a pacemaker are allowed);

The following exceptions are allowed: First degree atrioventricular (AV) block, second degree AV block Type 1 (Mobitz Type 1/Wenckebach type), or right bundle branch block.

15. Uncontrolled hypertension despite appropriate medical therapy (sitting blood pressure of greater than 160 mmHg systolic and/or 100 mmHg diastolic at 2 separate measurements no more than 45 minutes apart during the Screening visit). Patients may be re-screened after referral and further management of hypertension;
16. Hypotension, as indicated by systolic blood pressure < 84 mmHg on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming upright position;
17. Bradycardia as indicated by a heart rate of < 45 beats per minute on the ECG at the Screening or Baseline Day 1 visit;
18. Treatment with any investigational product within 28 days or 5 half-lives (whichever is longer);

    Exception: treatment for prostate cancer with any investigational products where the mechanism of action is testosterone lowering. In this circumstance, there must be a minimum 12-month treatment free interval.
19. *Removed*;
20. Previous treatment with relugolix in a clinical study;
21. Patient is a study site employee or is a primary family member (spouse, parent, child, or sibling) of a site employee involved in the conduct of the study;

22. Known gastrointestinal disease or procedure that could interfere with the oral absorption or tolerance of relugolix, including inability to swallow whole tablets or conditions that may interfere with absorption at the level of the small intestine. Examples of such conditions include but are not limited to Crohn's disease, gastric bypass, active peptic ulcer disease, and gastrectomy. The medical monitor should be contacted for any questions regarding this exclusion criterion;
23. Use or planned use of any medication listed in the prohibited medications table (see Section 5.10.1) without the appropriate washout period;
24. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
25. Has a prior (within 1 year of the Screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
26. Any other medical or psychiatric condition that, in the opinion of the investigator, would interfere with completion of treatment according to this protocol.
27. Weight ≥ 400 pounds (181 kg) or has a body mass index ≥ 50;

4.4. Other Eligibility Criteria Considerations

Patient eligibility may require additional or repeat assessments such as safety labs, vital signs, or ECG during the Screening Period.

To assess any potential impact on patient eligibility with regard to safety, the investigator is referred to the Investigator Brochure for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) used in this study.

4.5. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the Screening Period. Study site personnel will access the interactive voice/web recognition system (IWRS) to assign a screening identification number to a potential patient.

For patients who provide informed consent and subsequently do not meet eligibility criteria, or withdraw consent are considered screen failures and are not randomized. Study site personnel should ensure that the source record includes documentation for the screen failure (eg, medical history, eligibility criteria, procedures performed).

Patient numbers assigned to patients who become screen failures are not to be reused. Patient identification numbers will be assigned to eligible patients at randomization, as described in Section 4.6.

4.6. Method of Assigning Patients to Treatment Group and Patient Identification Number

After a patient is screened and the investigator determines that the patient is eligible for enrollment, the site staff will complete the Randomization Authorization Form and send it to the sponsor (Myovant Sciences GmbH) or sponsor designee per the instructions in the investigator site file. The sponsor (or designee) will approve the patient's enrollment in writing. Once the site has received approval, the patient may undergo the Baseline Day 1 visit. The site will randomize the patient to treatment by using the IWRS during the patient's Baseline Day 1 visit. The IWRS will assign the patient identification (ID) number. This number will identify the patient for the duration of the study. A study treatment kit number will be available at the site according to the randomization code.

4.7. Removal of Patients from Therapy

Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Week 49 visit on the Schedule of Activities. The End of Treatment is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.

Follow-up visits to assess safety will be performed in all study patients. If the patient plans to start alternative androgen deprivation therapy less than 30 days after the End of Treatment visit, the Safety Follow-up visit may occur earlier, before the start of the alternative androgen deprivation therapy. Testosterone recovery will be evaluated in approximately 100 patients randomized to relugolix and approximately 50 patients to leuprolide acetate who complete 48 weeks of study drug treatment and, in the opinion of the investigator, are candidates for intermittent androgen deprivation therapy and will not be offered alternative androgen deprivation therapy upon completion of study therapy. These patients will return for the 60- and 90-day follow-up Testosterone Recovery visits.

The safety and/or compliance events shown in Table 4-1 will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved.

Table 4-1 Removal of Patients from Treatment

Reason	Comment
Adverse event or intercurrent illness	Any intolerable adverse event to the patient that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued
Failed to meet eligibility criteria post randomization	If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health
Dose hold	Relugolix dose hold that exceeds 10 consecutive days

Reason	Comment
Patient not meeting criteria for testosterone suppression to castrate level	Patients with disease progression while on study drug, assuming adequate testosterone suppression (testosterone level ≤ 50 ng/dL [1.7 nmol/L]), may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide. For patients requiring other systemic antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.
Laboratory abnormality defined by protocol: ALT or AST > 8 x ULN; or ALT or AST > 5 x ULN and persists for more than 2 weeks; or ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or INR > 1.5; or ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)	If any of these liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status).
Confirmed QTc prolongation of more than 500 msec, in the absence of a pacemaker, as read by a cardiologist	If QTc prolongation of > 500 msec in the absence of a pacemaker occurs, the ECG must be repeated. Confirmed QTc prolongation, measured by Fridericia's formula [QTcF = QT/(RR^0.33)], will result in removal of the patient from treatment.
Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist that may be related to study drug treatment	
Gross noncompliance with protocol	Patients who are, in the opinion of the investigator or the medical monitor, non-compliant with the protocol's requirements
Patient decision	Patients may permanently discontinue study treatment at any time for any reason. Following study drug discontinuation, patients should attend the protocol-required safety follow-up visit.
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime as described in Section 10.3.3. The sponsor will terminate this study following completion of study objectives, or earlier if deemed necessary.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; INR, international normalized ratio; QTc, QT interval corrected for heart rate; QTcF, QT interval corrected for heart rate using the Fridericia formula; ULN, upper limit of normal

Once study drug has been discontinued, all study procedures outlined for the Week 49 visit will be completed as specified in the Schedule of Activities (Section 1.1). The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who withdraw from treatment will not be replaced.

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. Patients randomized to relugolix should be counseled to notify the investigator in the event of intercurrent illness to determine if the study drug treatment can be continued. Every effort should be made to ensure the patient's compliance with study drug treatment, including calling patients to reschedule missed visits.

In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should attempt at least 3 documented telephone calls and, if necessary, a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.8. Contraception/Pregnancy Avoidance

It is not known what effects relugolix has on human pregnancy or development of the embryo or fetus. Therefore, male patients should avoid impregnating a female partner.

A patient must use a condom if having sex with a pregnant woman. Patients must not donate sperm from first dose of study drug through 4 months after the last dose of study drug.

Nonsterilized male patients should use a male condom, either alone or in addition to effective methods of contraception used by a female partner of childbearing potential, through defined periods during and after study treatment as specified below. Examples of effective contraceptive methods include condoms, hormonal contraceptives, and intrauterine devices.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to one of the following:

- Use a male condom if having sex with a woman of childbearing age or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods for the female partner, and withdrawal are not acceptable methods of contraception.

5. TREATMENTS

5.1. Treatments Administered

Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg following a loading dose of 360 mg on Day 1, or leuprolide acetate 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) 3-M depot injection (plus antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator). Randomization will be stratified by geographic region, presence of metastatic disease, and age**.**

Approximately 915 patients will be enrolled in the study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region.

Study treatment is defined as either oral relugolix or leuprolide acetate injection (see Table 5-1).

Table 5-1 Description of MVT-601-3201 Study Drugs

	Study Treatment	
Product name:	Relugolix	Leuprolide Acetate 3-M Depot
Formulation description:	Round film coated pink tablet	
Dosage form:	Tablet	
Unit dose strength and dosage level:	120 mg, following a single-loading dose of 360 mg	22.5 mg (11.25 mg in Japan, Taiwan, and China)
Route of Administration / Duration	Oral / 48 weeks[a]	Subcutaneous or intramuscular / 48 weeks[a]

a. Duration of treatment is 48 weeks during the Treatment Period; the last leuprolide acetate injection occurs 12 weeks before the end of the Treatment Period.

5.2. Identity of Investigational Product

Relugolix has the chemical name N-(4-(1-(2,6-difluorobenzyl)-5-((dimethylamino)methyl)-3-(6-methoxy-3-pyridazinyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-6-yl)phenyl)-N'-methoxyurea.

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using the US Pharmacopeia and the National Formulary excipients.

5.3. Randomization and Stratification

Patients are assigned to one of 2 treatment arms in accordance with the randomization schedule using an integrated randomization system (IWRS).

At Baseline Day 1, patients will be randomized in a 2:1 ratio to one of the following treatment arms:

Treatment Arm	Randomized Treatment	Approximate Number of Patients
Arm A	Relugolix 360 mg (three 120 mg tablets) single oral loading dose on Day 1 followed by 120 mg orally once daily	610
Arm B	Leuprolide acetate, 22.5 mg 3-M depot[a] injection (or 11.25 mg in Japan, Taiwan, and China)	305

a. Antiandrogen is administered for the first 4 weeks or longer if indicated, in the opinion of the investigator.

Randomization will be stratified by geographic region, presence of metastatic disease, and age as follows:

- Geographic Region
  - Europe;
  - North and South America; or
  - Asia and Rest of World.
- Presence of Metastatic Disease
  - Metastatic disease diagnosed on locally-read imaging by abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) or bone scan at the time of the Baseline Day 1 visit; or
  - No evidence of metastatic disease by locally-read imaging.
- Baseline Age
  - ≤ 75 years old; or
  - > 75 years old.

5.4. Directions for Administration

Relugolix

Relugolix 120-mg tablet strength will be available as immediate-release film-coated tablets. These tablets will be presented in 45-tablet bottle packaging and dispensed to patients every 4 weeks at scheduled study visits.

All protocol-specific criteria for administration of study drug must be met and documented prior to study drug administration. Study drug will be dispensed by study personnel only to eligible patients who are under the supervision of the investigator or identified subinvestigator(s). If a blood draw or any study procedure coincides with a meal, the study procedure will take precedence, followed by the blood draw, and then the meal.

At the Baseline Day 1 visit, the site will administer a single loading dose of oral relugolix 360 mg (3 tablets).

Patients randomized to relugolix will be instructed to take one tablet on an empty stomach at least 1 hour before breakfast once daily. If the dose is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

Patients may consume water ad libitum. Patients should swallow the study medication whole and not chew it or manipulate it in any way before swallowing.

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK and pharmacodynamic samples are collected.

Leuprolide Acetate

Leuprolide acetate 3-M depot injection, 22.5 mg (or 11.25 in Japan, Taiwan, and China), will be administered every 12 weeks. Leuprolide acetate 3-M depot will be administered on Day 1 at the clinic, then at 12-week intervals (see Schedule of Activities, Section 1.1) and investigators should follow product instructions provided by the manufacturer. An antiandrogen may be administered for the first 4 weeks or longer if indicated, as determined by the investigator, and/or as indicated by disease status (eg, in patients with extensive localized symptomatic disease or with metastatic disease).

Possible antiandrogen options include, but are not limited to, bicalutamide, flutamide, and nilutamide.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that is related to study drug and cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted if the investigator believes it is in the best interest of the patient to interrupt relugolix dosing until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 10 consecutive days for evaluation and treatment of an adverse event. Patients may subsequently be re-started on study drug, with the written approval of the sponsor (or designee).

5.6. Dose Escalation, Dose Reduction, and Dose Interruption

Neither dose escalations nor dose reductions are allowed in the study.

Every effort should be made to continue relugolix administration through treatment-emergent adverse events unless they are grade 3 or 4 and related to study drug, or the investigator believes it is in the best interest of the patient to interrupt relugolix dosing. Of note, patients on leuprolide acetate 3-M depot injection continue to receive GnRH agonist therapy because it is impossible to discontinue treatment.

If the grade 3 or 4 adverse event improves to grade 0, 1, or 2 after holding the dose, or if the adverse event is no longer believed to be related to study drug, the patient may be rechallenged at the same dose at the discretion of the investigator and medical monitor. If the adverse event remains grade 3 or grade 4 after treatment discontinuation and the investigator continues to believe the adverse event is related to study drug, study drug treatment should be discontinued permanently.

5.7. Storage, Packaging, and Labeling

Relugolix will be packaged in bottles containing 45 120-mg tablets of relugolix. Additional details regarding the packaging of relugolix are provided in the Investigator Brochure and investigator site file.

Leuprolide acetate 11.25 mg or 22.5 mg 3-M depot injection will be packaged and labeled for clinical trial use.

Relugolix medication should be stored in an appropriate, limited-access, secure location, protected from light, in the original bottles and within a temperature range at 15°C to 25°C (59°F to 77°F) with excursions permitted up to 30°C (86°F).

A daily temperature log of the drug storage area must be maintained every working day.

Study drug must be stored under the conditions specified, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Patients will be instructed to store study drug at room temperature out of the reach of children.

Further guidance and information for final disposition of unused study drug are provided in the investigator site file. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Refer to the leuprolide acetate product labeling for information regarding the proper storage and handling of leuprolide acetate.

5.8. Blinding

Blinding is not applicable; this is a randomized open-label study.

5.9. Study Drug Accountability and Treatment Compliance

Patients should bring all unused study drug to each study visit. Study drug accountability will be conducted and results will be recorded as the primary source of study drug accountability. If a patient is persistently noncompliant with the study treatment, it may be appropriate to withdraw the patient from the study.

All patients should be reinstructed regarding dosing compliance during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance.

Patients randomized to relugolix should be counseled to notify the investigator in the event of intercurrent illness to determine if the study drug treatment can be continued. Should a patient need a surgery of any kind, please contact the medical monitor. Every effort should be made to ensure the patient's compliance with study drug treatment, including calling patients to reschedule missed visits.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-2 provides examples of systemic medications that are prohibited prior to the first dose of study medication until the End of Treatment visit and the Follow-up Period is complete. This list is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class. Patients may "wash out" of these prohibited medications prior to dosing based on the periods provided in Table 5-2.

Any investigational agent for the treatment of prostate cancer where the mechanism of action is testosterone lowering, including agents that are commercially available for indications other than prostate cancer that are under investigation for the treatment of prostate cancer, are also prohibited for at least 12 months prior to the first dose of study medication.

Table 5-2 Prohibited Medications and Washout Periods

Drug Class	Examples		Minimum Washout Period[c]
GnRH analogues	Leuprolide acetate injection[a] Goserelin acetate injection		At least one dosing interval of the depot preparation; minimum of 3 months[d]
GnRH antagonists	Degarelix		At least one dosing interval of the depot preparation; minimum of 3 months[d]
Antiandrogens[a]	Bicalutamide Flutamide	Nilutamide Enzalutamide[b]	3 months
CYP17 inhibitors	Abiraterone acetate + prednisone		3 months
Other androgen suppressing agents or androgens	Estrogens Ketoconazole Testosterones	Megestrol acetate Progestogens	3 months
5-alpha reductase inhibitors	Finasteride Dutasteride		4 weeks 6 months
Class IA an III antiarrhythmics	Amiodarone Procainamide	Quinidine Sotalol	2 weeks (3 months for amiodarone)

Drug Class	Examples		Minimum Washout Period[c]
Moderate and strong CYP3A and P-glycoprotein inducers	Bosentan Carbamazepine Efavirenz Etravirine Mitotane Modafinil Nafcillin	Phenobarbital Phenytoin Rifampin St John's Wort Primidone Rifabutin Rifapentine	1 week Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.
Moderate/strong P-glycoprotein inhibitors	Amiodarone Azithromycin Captopril Carvedilol Clarithromycin Conivaptan Cyclosporin Diltiazem Dronedarone Eliglustat Erythromycin	Felodipine Itraconazole Ketoconazole Lapatinib Lopinavir/Ritonavir Quercetin Quinidine Ranolazine Ticagrelor Verapamil	1 week (3 months for amiodarone) (3 months for ketoconazole) Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.
Herbal therapies	Chinese herbs Ginkgo biloba	Kava kava Ginseng	2 weeks or 5 half-lives (whichever is shorter)

Abbreviation: CYP, cytochrome P450

a. Unless randomized to leuprolide acetate control arm of this study. After randomization, antiandrogen therapy is permitted for the first 4 weeks or longer of leuprolide acetate treatment.
b. Enzalutamide is allowed for the treatment of castration-resistant disease that occurs on study (rising prostate-specific antigen in the setting of testosterone suppressed to castrate levels (≤ 50 ng/dL [1.7 nmol/L]).
c. Minimum washout period is calculated from the date of last dose of prohibited medication to the first day of study drug.
d. Patients with cumulative previous androgen deprivation therapy > 18 months are excluded, regardless of washout period.

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded. At a minimum, the drug generic name, dose amount, route of administration, start date, and stop date will be recorded in the source documents and the eCRF.

If alternative androgen deprivation therapy is initiated prior to 30 days after the last relugolix dose, record the alternative androgen deprivation therapy as a concomitant medication.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]), should be encouraged to remain on study and, if indicated, may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide. For patients requiring other systemic

antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.6. Further details of the procedures are provided in the investigator site file.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Section 1.1). The study is divided into 3 periods: Screening Period, Treatment Period, and Follow-up Period. Unscheduled visits may also occur as needed to evaluate patients.

6.2. Screening Period (Day -28 to Day -1)

The Screening Period will be from Day -28 through Day -1. At the Screening visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent before any study-specific procedures are conducted, unless the procedures are part of routine standard of care. The informed consent process must be documented in the patient's clinical record.

The investigator will assess and confirm the eligibility of each patient and determine that each patient will maintain study drug compliance during the treatment period. All screening procedures results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

The following assessments will be performed:

- Complete medical history, including detailed prostate cancer history;
- Vital signs, weight, and height;
- 12-lead ECG;
- ECOG performance assessment;
- Complete physical exam and visual acuity assessment;
- An abdominopelvic CT or MRI and a bone scan should be performed and read locally to determine the presence of metastatic disease within 60 days prior to randomization. However, if CT or MRI demonstrates presence of metastatic disease, a bone scan is not required. If metastatic disease is not present on CT or MRI, then a bone scan is also required.
- Demographics;
- Laboratory data collection (see Section 1.1);
- Verify inclusion/exclusion criteria; and
- Concomitant medications and adverse events.

A Randomization Authorization Form must be submitted to the sponsor for approval prior to conducting the Baseline Day 1 visit.

6.3. Treatment Period (Day 1 to Week 49 [Study Day 337])

Baseline Day 1 Visit

Study site personnel should ensure that an approved Randomization Authorization Form is in the patient's file before proceeding with the randomization and Day 1 visit procedures. Patients will be randomized to either relugolix or leuprolide acetate 3-M depot injection 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) (see Section 5.3).

The following assessments will be performed:

- Patient-reported outcome questionnaires (EQ-5D-5L, EORTC-QLQ-PR25, and EORTC-QLQ-C30)
  - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Medical history;
- Vital signs and weight;
- 12-lead ECG;
- ECOG performance assessment;
- Symptom-based physical examination;
- Verify inclusion/exclusion criteria;
- Concomitant medications and adverse events;
- Randomize the patient;
- Laboratory collection (see Section 1.1); and
- Study drug management:
  - If study drug administration is not logistically feasible on the same day as randomization, Day 1 will be defined as the day of the first dose.
  - If the patient is randomized to relugolix, site personnel will administer a single loading dose of oral relugolix 360 mg (3 tablets) and then dispense study drug to the patient and instruct on daily dosing of 120 mg (1 tablet) and the importance of medication compliance (see Section 5.4);
  - If the patient is randomized to leuprolide acetate, site personnel will administer the injection in the clinic.

Day 4 and Weeks 2 and 3 Visits (Visit Window ± 2 days)

The following assessments will be performed:

- Vitals signs;
- Laboratory collection (see Section 1.1); and
- Concomitant medications and adverse events.

Note: The Week 2 visit will only occur for patients who are part of the Japan or China subset for PK analysis.

Weeks 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, and 45 Visits (Visit Window ± 7 Days)

Importantly, patients randomized to relugolix should be called 7 days before each visit to ensure the patient is compliant with study drug medication.

The following assessments will be performed:

- Patient-reported questionnaires will be completed on the electronic tablet provided (Weeks 5, 13, 25, and 37 only)
    - Patients will complete the questionnaires before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs, weight
    - Weight will be collected only on Weeks 13 and 25;
- 12-lead ECG (Weeks 5, 13, and 25 only);
- ECOG performance assessment (Week 25 only);
- Symptom-based physical examination (except Week 25);
- Complete physical exam and visual acuity assessment (Week 25 only);
- Laboratory collection (see Section 1.1)
    - Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose, approximately 24 hours after the previous dose. Patients may be dosed in the clinic at these visits, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing.
- Concomitant medications and adverse events; and
- Study drug management:
    - For patients randomized to relugolix,
        - Perform study drug accountability;
        - Dispense study drug. Patients may be dosed in the clinic, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing;
        - Remind patients on importance of medication compliance.
    - For patients randomized to leuprolide acetate,
        - Site will administer leuprolide acetate in clinic every 12 weeks (Weeks 13, 25, and 37).

Week 49 or (Early Termination of Study Drug) (Visit Window ± 7 Days)

- For patients receiving relugolix, a member of the site team will call the patient 7 days before the Week 49 visit to remind the patient of the need for compliance with their study medication;
- Patient-reported outcome questionnaires
    - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs, weight;
- 12-lead ECG;
- ECOG performance assessment;
- Complete physical exam and visual acuity assessment;

- Laboratory collection (see Section 1.1);
    - Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose, approximately 24 hours after the previous dose.
- Concomitant medications and adverse events; and
- Study drug management:
    - For patients randomized to relugolix,
        - Perform study drug accountability.

6.4. Follow-up Period

The study day in which the Follow-up visit occurs is relative to when the patient takes his last dose of study drug. The End of Treatment is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.

30-Day Safety Follow-up Visit (Visit Window ± 7 Days)

A Safety Follow-up visit should occur 30 days after the End of Treatment and may occur earlier for patients who are starting alternative androgen deprivation therapy or do not complete 12 weeks of study treatment. Adverse events should continue to be collected and recorded through 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Serious adverse events and concomitant medications will be collected from the signing of the informed consent form until the Safety Follow-up visit approximately 30 days after the last dose of study drug.

All other study procedures should be completed before the start of alternative androgen deprivation therapy.

The following assessments will be performed:

- Patient-reported questionnaires
    - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs and weight;
- 12-lead ECG;
- ECOG performance assessment;
- Symptom-based physical examination;
- Laboratory collection (see Section 1.1); and
- Concomitant medications and adverse events.

Testosterone Recovery Visit (Visit Window ± 7 Days)

Patients who have started alternative androgen deprivation therapy will not participate in the 60- and 90-day follow-up visits. Approximately 100 patients randomized to receive relugolix and approximately 50 patients randomized to receive leuprolide acetate who complete the 48 weeks of study drug treatment and, in the opinion of the investigator, are candidates for intermittent androgen deprivation therapy will be included in the Testosterone Recovery 60- and 90-day Follow-up visits. These patients will discontinue relugolix after 48 weeks of treatment and will be offered a period off androgen deprivation therapy.

The following assessments will be performed:

- Patient-reported outcome questionnaires
  - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs;
- Symptom-based physical examination;
- Laboratory collection (see Section 1.1); and
- Concomitant medications.

Health Status Survey

During the final weeks prior to database lock, sites will be asked to contact all study participants or their immediate family regarding the current health status of previously enrolled/completed study patients. If the site is unsuccessful in contacting the patient and/or immediate family, the site may access hospital records or publicly available sources such as national registries, newspaper obituaries, and social networking websites.

6.5. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The following activities should be completed at an Unscheduled visit: recording of the date and reason for the visit in the patient's source documents, concomitant medication review and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment and collection of a PK sample if indicated, 12-lead ECG, study drug compliance and dispensation, etc. may be conducted as needed. See Schedule of Events (see Section 1.1) for tests that may be performed if indicated at an unscheduled visit. Consult with the medical monitor, if needed, to discuss Unscheduled visit testing.

6.6. Study Procedures

6.6.1. Efficacy-Related Procedures

6.6.1.1. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, testosterone, dihydrotestosterone, sex hormone binding globulin, and PSA will be collected predose at the visits indicated in the Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. Testosterone samples may be analyzed at a second laboratory to confirm non-castrate levels (Section 1.1).

Serum LH, FSH, dihydrotestosterone, sex hormone binding globulin, and PSA samples will be analyzed at a central laboratory.

PSA will also be used to evaluate biochemical progression per Prostate Cancer Clinical Trials Working Group 3 guidelines [Scher, 2016].

Analysis of serum samples for testosterone is detailed below:

Testosterone Assessment

Serum concentrations of testosterone will be obtained as indicated in the Schedule of Activities (see Section 1.1).

Testosterone will be assayed using a liquid chromatography-tandem mass spectrometry method sensitive at least as low as 5 ng/dL (0.17 nmol/L) for all measurements.

Between Week 5 and Week 49 visits (inclusive), testosterone samples that are above castrate level (> 50 ng/dL) will be reported to the investigator at the respective study site. Testosterone samples may be subject to reanalysis by liquid chromatography/mass spectrometry and/or immunoassay sensitive to at least as low as 10 ng/dL.

Instructions for collection and processing of blood specimens are provided in the investigator site file.

6.6.1.2. Pharmacokinetic Sample Collection

Relugolix

Pharmacokinetic samples will only be collected in patients randomized to relugolix study drug.

Blood samples for pharmacokinetic analysis of relugolix will be collected at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients may take their dose of study drug in the clinic at these visits. Study drug will be administered on an empty stomach or at least 2 hours before food, and food will be withheld for 1 hour after dosing. The date and time of their previous dose of study drug (ie, the dose the day before the clinic visit) will be accurately recorded.

Ideally, predose samples should be collected approximately 24 hours (±6 hours) after the previous dose of relugolix, although samples collected outside of this window would not be considered a protocol deviation.

If the study patient inadvertently took the study drug at home on the morning of the clinic visit, the date and time of that dose should also be accurately recorded and the pharmacokinetic sample collected, which may be used for population PK modeling.

Plasma from the Week 5 and Week 13 visits in all patients will be analyzed for relugolix plasma concentration. Analysis of other individual patient plasma samples will be performed on a case-by-case basis (such as those patients with non-castrate testosterone levels).

Collection, processing, storage, and shipping instructions will be provided in the investigator site file. Plasma analysis of relugolix will be performed by the sponsor (or designee).

Leuprolide Acetate

For patients on leuprolide acetate, in the event of non-castrate testosterone levels, a blood sample may be taken for potential analysis of leuprolide acetate plasma concentration, following discussion with the medical monitor

China and Japan Pharmacokinetic Subset

In a subset of patients from China (if enrolled) and approximately 20 patients from Japan that are randomized to relugolix, additional relugolix PK samples will be collected on Day 1, Day 4, and Week 2 visits (see Schedule of Activities in the protocol synopsis, Section 1.1). The actual date and time of study drug administration and the date and time of each PK sample will be accurately recorded.

All samples from the China and Japan subset will be analyzed for plasma relugolix concentrations. Collection, processing, storage, and shipping instructions will be provided in the investigator site file. Plasma analysis of relugolix will be performed by the sponsor (or designee).

6.6.1.3. Pharmacogenomics Sample Collection

Whole Blood Sample for Germline Deoxyribonucleic Acid

Pharmacogenomic analysis may be conducted to examine the contribution of genetic variance on drug response, for example, its efficacy and safety. Participation of study patients in pharmacogenomic sample collection is optional. A pharmacogenomics sample will be collected from patients at all participating study centers, with individual patient consent and per local ethics and regulatory standards. The sample will be retained for germline deoxyribonucleic acid (DNA) analysis of potential genetic determinants of drug safety, drug efficacy or disease response, and drug metabolism.

Every patient must sign informed consent/be consented in order to participate in the sampling of whole blood for DNA analysis. This research may be used to develop a better understanding of the safety and efficacy of relugolix and other study drugs, to increase understanding of the disease/condition being studied, and for improving the efficiency, design and study methods of future research studies.

Two venous whole blood sample (4 mL per sample) for the analysis of germline DNA will be collected at Day 1 from all patients who have provided informed consent. The DNA samples are expected to be collected at the Day 1 visit, but if necessary, may be collected at any visit after randomization. If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible. Germline DNA analysis may be conducted to investigate the contribution of genetic variance on drug response, for example, its efficacy and safety. As pharmacogenomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples.

Individual blood samples for germline DNA analysis, including the result of any analyses and corresponding information will be identified only by a code in a computer database.

The whole blood samples for DNA analysis will be stored securely at the sponsor's location or its designated central laboratory vendor until 10 years after completion of this study (HERO, MVT-601-3201) and/or until the drug development of relugolix is no longer actively pursued by Myovant or its collaborators. The storage period for these samples may be adjusted by country in accordance with local regulatory and/or legal requirements for the storage of research samples.

Such changes will be reflected in the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) country-specific informed consent form. After that time, the samples will be properly destroyed by the central laboratory or designee following approval by the sponsor. The investigator will keep records linking the patient identity with the samples for the time required by applicable law. Patients who consent and provide a pharmacogenomic sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time.

Directions for sample collection and handling can be found in the investigator site file.

6.6.1.4. Quality of Life

European Quality of Life 5-Dimension 5-Level Assessment

The EuroQol EQ-5D-5L comprises 5 scales and an overall assessment of health status on a visual analogue scale (Appendix 2). The 5 scales include: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The original version, the EQ-5D-3L, includes 3 response options for each scale. However, a new 5-level response-option version, the EQ-5D-5L, has been developed with the following response options: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. It is believed that the EQ-5D-5L is superior to the EQ-5D-3L in terms of feasibility, ceiling effects, discriminatory power, and convergent validity. The EQ-5D-5L index values will be calculated from the EQ-5D-5L descriptive system scores based on the Crosswalk value sets [EuroQol Group, 1990; Brooks, 1996; Herdman, 2011; Janssen, 2013].

European Organisation for Research and Treatment of Cancer Assessments

The EORTC-QLQ-C30 [Fayers, 2001; Fayers, 2002] (Appendix 3) and the 25-item prostate cancer module EORTC-QLQ-PR25 [Spry, 2006] (Appendix 4) will be administered as specified in the Schedule of Activities (see Section 1.1).

The EORTC QLQ-C30 core measurement will be used to capture distal outcomes, including physical, social functioning, and overall health-related quality of life. The QLQ-C30 core questionnaire incorporates 30 questions comprising 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality of life scale. Several single-item symptom measures are also included. It is a reliable and valid measure of health-related quality of life in patients with cancer and takes about 11 minutes to administer. The instrument has been validated and used in many countries [Aaronson, 1993].

The EORTC-QLQ-PR25 is the 25-item Prostate Cancer module (P25) of the EORTC. The EORTC-QLQ-PR25 contains 3 additional symptom scales (urinary, bowel, sexual) and 5 treatment-related items.

6.6.2. Safety-Related Procedures

6.6.2.1. Weight, Height, and Body Mass Index

Height and weight will be measured during screening (within 28 days before the first dose of study drug). Weight will be obtained at additional time points as specified in the Schedule of

Activities (see Section 1.1). Patients should have weight and height measured while wearing indoor clothing and with shoes removed.

6.6.2.2. Vital Signs

Vital sign measurements include temperature, pulse rate, and seated measurement of diastolic and systolic blood pressure. For each patient, temperature should be recorded using the same modality throughout the entire study. Patients should be sitting at rest for 5 minutes before blood pressure is measured. When vital sign measurements are scheduled at the same time as an ECG and blood draw, the vital signs, when possible, will be obtained immediately prior to the ECG and blood draw, and the blood draw will be collected at the scheduled time.

6.6.2.3. Physical Exams and Visual Acuity

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart, and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the baseline assessment.

Visual acuity will be evaluated at Screening, Week 25, and Week 49 by a standard visual eye chart. Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, he should wear his usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions (see the investigator site file for additional details).

Patients whose presenting visual acuity score is 90 or lower at the screening visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, i.e., an ophthalmologist or an optometrist. Any findings (i.e., diagnoses) from the eye examination should be recorded as medical history.

Patients whose presenting visual acuity score at Week 25, Week 49, or Early Termination has decreased by 10 or more points from the screening visit must be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.

6.6.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the investigator site file and the protocol Schedule of Activities (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the patient ID number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Metabolic Panel**
Hematocrit Hemoglobin Leukocytes with differential Neutrophils and absolute neutrophil count Platelet (count)	Albumin Alkaline phosphatase ALT AST Bilirubin (total) Blood urea nitrogen Calcium Carbon dioxide Creatinine Chloride Serum gamma-glutamyl transferase Glucose Lactate dehydrogenase Magnesium Phosphate Potassium Sodium Urate	Total cholesterol High density lipoprotein cholesterol Low density lipoprotein cholesterol Triglycerides Hemoglobin A1c
Endocrine Panel	**Diagnostic Screening (investigator's discretion)**	
Serum testosterone Serum LH Serum FSH Serum sex hormone binding globulin	Hepatitis panel, according to CDC criteria	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FSH, follicle-stimulating hormone; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; LH, luteinizing hormone

A separate sample will be collected at the Day 1 visit and will be banked and tested for presence of hepatitis A, B, and C (hepatitis A antibody, IgM, hepatitis B core antibody, IgM, hepatitis B surface antigen, and hepatitis C antibody) if requested by the medical monitor for evaluation of abnormal liver function tests.

The central laboratory will perform laboratory tests for chemistry, hematology, and plasma and serum hormone levels.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

6.6.2.5. 12-Lead Electrocardiograms

A 12-lead ECG will be administered at the time points specified in the Schedule of Activities (Section 1.1). When an ECG is scheduled at the same time as vital signs and a blood draw, the ECG, when possible, will be obtained after the vital signs and prior to the blood draw; the blood draw will be collected at the scheduled time. ECGs will be read locally by a qualified physician.

If patients have a prolonged QTc (> 500 msec) in the absence of a pacemaker, the ECG should be repeated and confirmed. Patients with a confirmed QTc > 500 msec, measured by Fridericia's formula [QTcF = QT/(RR^0.33)], should be withdrawn. All abnormal ECG findings must be documented by the investigator as clinically significant or not.

6.6.2.6. Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient 30 days prior to the first dose of study drug until 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection will recorded in the eCRF (Exception: amiodarone will be reported if taken within 3 months prior to the first day of study drug). See Section 5.10.1 for a list of medications and therapies that are prohibited and/or allowed during the study.

6.6.2.7. Radiologic Assessment

CT imaging or MRI of the abdominopelvic region with contrast and a bone scan must be obtained prior to randomization for each patient to determine the presence or absence of metastatic disease. The scans should be read locally and do not need to be repeated if a scan exists within 60 days prior to the Baseline Day 1 visit. However, if CT or MRI demonstrates presence of metastatic disease, a bone scan is not required. If metastatic disease is not present on CT or MRI, then a bone scan is also required.

Radiologic assessment is not included as part of the Schedule of Activities after randomization.

6.7. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of 8 mL of whole blood for pharmacogenomics testing (see Section 6.6.1.3) will be collected.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of his sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations including visual acuity assessment, vital signs, weight, ECGs, and clinical laboratory tests.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention; or
    - Requires interruption or discontinuation of study drug.

Events that **do not** meet the definition of an adverse event include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- The disease/disorder being studied, or expected progression;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen; and
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent).

Adverse events that occur during the study should be evaluated by the investigator and graded according to CTCAE (Appendix 5). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous". Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of study drug are permitted; however, study drug can be held for a period of up to 10 days for evaluation

and treatment of an adverse event. The study drug may be restarted if deemed safe for the patient by the investigator.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events that jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local IRB/IEC.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's answers to the EQ-5D-5L will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in a partner will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered until the Safety Follow-up visit approximately 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first.

Serious adverse events will be collected from the signing of the informed consent form until the Safety Follow-up visit approximately 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

Any event occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who

continues to meet eligibility criteria and proceeds to dosing with study drug; the exception to this includes procedure-related pretreatment-emergent events which should be recorded as adverse events in the electronic data capture (EDC) system for those patients who remain eligible for study participation.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The definitions in Table 7-1 are to be used for the relationship of the adverse event to study drug.

Table 7-1 Causal Relationship to Study Drug

Relationship	Criteria
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (re-challenge) or withdrawal (de-challenge).
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE (see Appendix 5). For terms not specified with the CTCAE, the criteria in Table 7-2 should be used to determine the grade severity.

Table 7-2 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized Treatment Period or the Follow-up visit should be reported to the sponsor using the serious adverse event form within 24 hours of the study site personnel's knowledge of the event (see Section 7.6), even if the event does not meet serious adverse event criteria. Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 6.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or international normalized ratio (INR) >1.5
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1) AST or ALT increases to ≥ 3 x ULN; AND
2) Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3) Alkaline phosphatase value does not reach 2 x ULN; AND
4) No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease;
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus);
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
   - Alcoholic hepatitis;
   - Nonalcoholic steatohepatitis; or
   - Autoimmune hepatitis.

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

Using a serious adverse event report form, all serious adverse events must be reported **within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose or pregnancy of partner is available on the serious adverse event report form and is as follows:

Send completed Safety Report Forms to IQVIA (previously named QuintilesIMS; contact information as below and on the SAE Form):

Site Location	E-mail (Primary reporting method)	Fax Number (Secondary reporting method)
All Regions	PPD	PPD

For questions on Serious Adverse Event (SAE)/Adverse Event of Clinical Interest or events of overdose reporting, please call:

- North/South America: PPD
- Regional toll-free phone and fax lines distributed separately. Please refer to the investigator site file.

The initial report should include:

- Study number (MVT-601-3201);
- Site address and number;
- Investigator name;
- Patient ID number, sex, and age;
- Details of study drug administration;
- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity); and
- Causal relationship to the study drug.

If the patient died, the report should include the cause of death and whether or not the cause of death was related to study drug, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 240 mg within a 24-hour window is an overdose, except for the 360-mg loading dose. The sponsor does not recommend specific treatment for an overdose; supportive treatment should be provided as clinically applicable.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis); and

- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If the partner of any patient becomes pregnant during the study or through 4 months after the last dose of study drug, the investigator must inform the sponsor of the pregnancy.

The patient should remain on study drug treatment, unless otherwise indicated.

If the patient agrees, the patient's pregnant partner should be notified and requested to sign a Release of Information form, permitting transfer of information regarding the pregnancy and outcome to the sponsor.

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the partner pregnancy report forms. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Benefit/Risk Assessment

Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

The risk assessment and mitigation strategies for this protocol are outlined in Table 7-3.

Table 7-3 Relugolix Potential Risks and Mitigation

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Stopping Criteria**
Hepatic Enzyme Increases Isolated increases in hepatic enzymes have been observed in prior clinical studies. Hepatic enzyme increases, considered an important potential risk of treatment with relugolix, are closely monitored in accordance with FDA guidelines for assessing drug-induced liver injury [FDA, 2009] in all relugolix studies.	Exclusion criteria for AST and ALT > ULN; total bilirubin values > ULN unless consistent with Gilbert's syndrome.	Liver chemistry will be monitored during the study. Appropriate liver stopping criteria and follow-up procedures are detailed in Section 7.5.2.
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Stopping Criteria**
evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.		acuity will be evaluated during the study.
Risks Associated with Medical Castration Acute and subsequent chronic symptoms of medical castration (reduction of testosterone to ≤ 50 ng/dL [1.7 nmol/L]) include vasomotor symptoms or hot flushes, disturbed sleep related to vasomotor symptoms, decreased libido, and fatigue or loss of energy. These side effects are usually not severe and can be managed with anticipatory guidance. Long-term suppression of testosterone is associated with well-characterized risks including bone loss, decreased muscle mass, possible changes in insulin sensitivity with increased risk of diabetes, altered lipid metabolism, and possible increased risk of cardiovascular disease [Oefelein, 2002; Lopez, 2005; Diamond,1998; Keating, 2006; Braga-Basaria, 2006; Saigal, 2007; Tsai, 2007; D'Amico, 2007; Efstathiou, 2009].	-	Effects can usually be managed with appropriate anticipatory guidance (eg, diet and exercise programs) or supportive therapy when required (eg, lipid-lowering or bone-sparing agents).
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	-	Fasting lipids and glucose will be monitored during the study.
Loss of Bone Mineral Density Loss of bone mineral density is considered a potential risk of treatment with relugolix in the prostate cancer indication.	-	Fractures will be assessed through adverse event monitoring. Use of anti-resorptive bone therapy, such as bisphosphonates or denosumab, may be considered by the treating physician.

Abbreviations: ALT; alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; FDA, Food and Drug Administration; PLD, phospholipidoses; ULN, upper limit of normal

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the investigator site file with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and Good Clinical Practices. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

8.3. Independent Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will review available safety data, as appropriate, on a periodic basis throughout the conduct of the study. Details of the Data and Safety Monitoring Board will be captured in a charter prior to the start of the study.

8.4. Steering Committee

A Steering Committee consisting of experts in the field of prostate cancer and staff members of Myovant Sciences GmbH will be established to provide oversight for the clinical trial, study design, study conduct, data analysis, and presentation and publication of the study data. Details of the Steering Committee responsibilities will be captured in a separate charter.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan will describe the detailed statistical methods and analyses for this study. The statistical analysis plan will be prepared and finalized prior to database lock and analysis of the primary and secondary endpoints.

All confidence intervals will be 2-sided at an alpha level of 0.05 unless otherwise specified. The methodology to be used to maintain a study-wide type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 2:1, relugolix to leuprolide acetate 3-M depot. Randomization will be stratified by the following factors:

- Geographic Region: North and South America versus Europe versus Asia and Rest of World;
- Presence of Metastatic Disease: yes versus no;
- Baseline Age: $\leq$ 75 years old versus > 75 years old.

Stratified efficacy analyses will incorporate these 3 stratification factors unless otherwise specified.

9.2. Analysis Populations

The Intent-To-Treat (ITT) population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. This will be the primary population used for the efficacy analysis. Patients will be analyzed according to their randomized treatment assignment.

The Per-Protocol population will consist of those members of the ITT population who have no major protocol deviations as defined in the statistical analysis plan, considering the following protocol deviations but not limited to:

- Those who entered the study even though they did not satisfy the entry criteria;
- Those who developed withdrawal criteria during the study but were not withdrawn;
- Those who received the wrong treatment or incorrect dose;
- Those who received an excluded concomitant treatment.

The Per-Protocol population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT population. The Per-Protocol population will be used as a sensitivity analysis of the ITT population for the primary efficacy endpoint and secondary endpoints. The Per-Protocol population will be identified prior to the database lock.

The primary population for safety analyses will be the Safety population, defined as all patients who receive at least one dose of any study treatment. Patients will be analyzed according to the treatment actually received, regardless of their randomized treatment assignment.

9.3. Efficacy Analyses

9.3.1. Primary Endpoint Analyses

The primary efficacy endpoint is the sustained castration rate, defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 (Study Day 337). This probability will be estimated for each treatment group using the Kaplan-Meier method with the confidence interval calculated using the exponential Greenwood formula via log-log transformation of the survival function. Patients who discontinue treatment prior to observing a testosterone level > 50 ng/dL (1.7 nmol/L) will be censored at the last testosterone assessment prior to discontinuation. Detailed censoring rules will be described in the statistical analysis plan.

There are 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit:

- Evaluation Criterion 1: to determine whether the sustained castration rate for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion.
- Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion. The confidence interval of the treatment difference will be calculated using the formula $\hat{V}\left[\widehat{S_1}(t) - \widehat{S_2}(t)\right] = \hat{V}\left[\widehat{S_1}(t)\right] + \hat{V}\left[\widehat{S_2}(t)\right]$, where each of the variance of the Kaplan-Meier estimate will be calculated using the Greenwood's formula $\hat{V}\left[\hat{S}(t)\right] = \hat{S}(t)^2 \left[\sum_{j:t_{(j)} \le t} \frac{d_j}{n_j(n_j - d_j)}\right]$; n_j denote the number of patients at risk at time $t_{(j)}$ and d_j denote the number of events observed at time $t_{(j)}$) [Lachin, 2000].

The evaluation criteria used for the primary efficacy endpoint assessment will be determined by regional regulatory requirements and will be prespecified in separate regional statistical analysis plans. The 2-sided type I error rates for the final analyses will be controlled at 0.05 separately for each regional analysis.

9.3.2. Secondary Endpoint Analyses

If the result of the primary endpoint is statistically significant, the secondary endpoints will be analyzed. The methods and procedures necessary to maintain a study-wide 2-sided type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

- Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing at Week 1 Day 4, and prior to dosing at Week 3 Day 1 will be summarized by treatment group using the Kaplan-Meier method;
- Profound castration rate defined as the cumulative probability of testosterone suppression of ≤ 20 ng/dL (0.7 nmol/L) while on treatment from Week 25 Day 1 through Week 49 Day 1 will be estimated for each treatment group using the Kaplan-Meier method. The difference in the cumulative probabilities between the relugolix group and the leuprolide acetate group will be provided, along with the 95% confidence interval calculated in the same manner as in the primary analysis of the primary endpoint;
- PSA response and percent change from baseline in PSA at Week 3 and Week 5 will be summarized and compared between the relugolix group and the leuprolide acetate group;
- Proportions of patients who have a PSA concentration < 0.2 ng/mL (0.2 µg/L) at Week 25 will be summarized by treatment group. The proportions will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in proportions;
- Time to testosterone recovery in approximately 100 patients randomized to relugolix and approximately 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last received leuprolide acetate 3-M depot injection) will be compared between the relugolix group and the leuprolide acetate group;
- Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains will be summarized by treatment group. The least square means at Week 49 will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in the least square means using a mixed model for repeated measures;
- Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as EQ-5D-5L will be summarized by treatment group. The least square means at Week 49 will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in the least square means using a mixed model for repeated measures;
- Time to PSA progression;
- Proportion of patients with confirmed PSA progression among those who have achieved sustained testosterone suppression during the 48-week treatment.

Further details of the secondary analyses will be described in the statistical analysis plan.

9.4. Safety Analyses

The safety analyses will be based on the Safety population. Safety will be assessed by summarizing and analyzing adverse events, laboratory analytes, vital signs, ECG parameters, and concomitant medications.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ class using MedDRA 19.1 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used for analyses. The National Cancer Institute CTCAE will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the baseline versus post-baseline results.

9.5. Pharmacokinetic Analyses

Plasma relugolix concentrations will be listed and summarized and included in the clinical study report.

PK data may be pooled with data from other studies in healthy male patients and patients with prostate cancer for population PK analysis, including evaluation of covariates of relugolix PK parameters, and for input into a population PK/pharmacodynamics models describing the relationship between relugolix exposure and serum testosterone [Ahsman, 2016]. These population PK analyses will be detailed further in a separate statistical analysis plan and report.

For patients from China (if enrolled) and Japan in the PK subset, plasma relugolix PK parameters C_{max}, $AUC_{0-\tau}$, and t_{max} from Day 1 and Day 14 of dosing will be determined. Population PK or PK/pharmacodynamic analyses may be conducted to explore the factors that affect relugolix exposure or to contribute to the assessment of the relationships between exposure and testosterone.

9.6. Endocrine Marker Analyses

Endocrine markers will be analyzed to see effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for:

- LH at Day 4, Week 5, Week 25, and Week 49 visits and/or follow-up visit(s);
- FSH at Day 4, Week 5, Week 25, and Week 49 visits and/or follow-up visit(s);

- Dihydrotestosterone at Week 5, Week 25, and Week 49 visits and/or follow-up visit(s);
- Sex hormone binding globulin at Week 5, Week 25, and Week 49 visits and/or follow-up visit(s).

9.7. Exploratory Analyses

Overall survival: Overall survival defined as time from randomization to date of death prior to data cutoff date. Kaplan-Meier methods will be used to describe survival distributions for each treatment arm.

Pharmacogenomic analyses may be conducted to examine the contribution of genetic variance on drug response, for example, its efficacy and safety, pending availability of samples. Polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix. These analyses will be detailed in a separate statistical analysis plan and associated reports.

9.8. Interim Analyses

There will be no planned interim efficacy analysis for the study.

9.9. Sample Size

To calculate the sample size required for the primary efficacy endpoint of this study, the following assumptions have been made:

- True probabilities of sustained testosterone suppression are 94% and 96% for relugolix and leuprolide acetate, respectively;
- 2:1 randomization ratio (relugolix:leuprolide acetate); and
- Dropout rate of 15%.

The assumed probability of sustained testosterone suppression for relugolix arm is 94%. It was estimated based on the predicted dose-response relationship for the effect of relugolix on testosterone suppression in patients with prostate cancer (data from phase 2 studies C27002 and C27003). The assumed castration rate of 96% for leuprolide acetate was based on the results from degarelix phase 3 registration program [Shore, 2013].

For Evaluation Criterion 1, 610 patients in the relugolix group will provide approximately 90% power to rule out a fixed probability of sustained testosterone suppression of < 90% at a 2-sided type I error rate of 0.05.

For Evaluation Criterion 2, with the non-inferiority margin of -10% and an overall 2-sided type I error rate of 0.05, a total of approximately 915 patients (610 relugolix, 305 leuprolide acetate) will yield at least 99% power in declaring the non-inferiority of relugolix compared to leuprolide acetate.

The final analysis will be performed separately for individual evaluation criterion using data collected through 48 weeks after enrollment of approximately 915 patients.

Approximately 915 patients will be randomized in order to fulfill the regulatory requirements of all participating countries.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a US investigational new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) Part 312, subpart D, "Responsibilities of sponsors and investigators," 21 CFR Part 50, and 21 CFR Part 56, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR Part 54, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

A properly executed, written informed consent, in compliance with the Declaration of Helsinki, ICH Good Clinical Practice, US CFR for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27), and local regulations, will be obtained from each patient before entering the patient in the trial. The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

The investigator will provide copies of the signed informed consent form to each patient (or to the patient's legal representatives) and will maintain the signed original document within the patient's record file per local requirements. The investigator will also fully document the informed consent process in the patient's source records.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator Brochure, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories:

1) Investigator's study file: The investigator's study file will contain the Investigator Brochure, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents: The required source data should include the following for each patient:
   - Patient identification (name, date of birth, gender);

- Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
- Participation in the study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
- Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
- Concomitant medication (including start and end date); and
- Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the Investigator Brochure, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.5. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on the 1572 form and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization Screening Period if an eCRF was initiated). If a patient withdraws from the study, the reason

must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.6. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability including dates and lot numbers of all study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, patient ID number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

All records must be made available to the sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

Current ICH Good Clinical Practice guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (eg, pharmacist), and the following:

- That such deliveries are recorded, for example, on the sponsor-approved drug accountability log, or other sponsor-approved pharmacy log;
- That study drug is handled and stored safely and properly in accordance with the study protocol;
- That study drug is only dispensed to study patients in accordance with the protocol;
- That any unused study drug is returned to the sponsor-designated facility or standard procedures for the alternative disposition of unused study drug are followed and only after approval by the sponsor representative.

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drug to any persons except the patients in this study;
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs;

- The investigator/pharmacist will maintain a study drug inventory. The inventory will include details of material received and a clear record of when they were dispensed and to which patient;
- The investigator/pharmacist agrees to conduct a final drug supply inventory on the drug accountability record at the conclusion or termination of the study. It must be possible to reconcile delivery records with those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries must be signed by the person responsible;
- Used or unused study drug may be destroyed at the study site according to standard institutional procedures if the sponsor agrees with the procedure, and after drug accountability has been conducted by the sponsor or representative. Unused study drug not destroyed at the site must be returned to the sponsor-designated facility at the end of the study or upon expiration.

10.1.7. Inspections

During the course of the study and after study completion, it is likely that one or more quality assurance audits will be undertaken by authorized sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the protocol as well as recognized Good Clinical Practice guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed time. By signing this protocol, the investigator grants permission to the sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.8. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of

emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers (eg, http://www.clinicaltrials.gov) before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH Good Clinical Practice guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may terminate the study and send a written notice of the termination along with the reasons to the investigator. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants' interests.

If the investigator intends to terminate participation in the study, the investigator must immediately inform the sponsor and provide the reason to it.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

Ahsman M, Faessel HM, Snelder NS, MacLean D, Vis P. Modelling and simulation of oral GnRH Antagonist TAK-385 and testosterone-lowering response in Prostate Cancer Patients to Optimize Trial Design and Dose Selection. Population Analysis Group Europe. 2016; Abstr 5847. Available at: http://www.page-meeting.org/print_abstract.asp?abstract_id=5847. Accessed: 11 January 2017.

Bosland MC. Testosterone treatment is a potent tumor promoter for the rat prostate. Endocrinology. 2014 Dec;155(12):4629-33.

Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, Basaria S. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol. 2006 Aug 20;24(24):3979-83.

Brooks R. EuroQol: the current state of play. Health Policy. 1996 Jul;37(1):53-72.

Cersosimo RJ, Carr D. Prostate cancer: current and evolving strategies. Am J Health Syst Pharm. 1996 Feb 15;53(4):381-96; quiz 446-8.

Conn PM, Crowley WF Jr. Gonadotropin-releasing hormone and its analogues. N Engl J Med. 1991 Jan 10;324(2):93-103.

D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ, Lamb DS, Joseph D, Tai KH, Malone S, Ludgate C, Steigler A, Kantoff PW. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol. 2007 Jun 10;25(17):2420-5.

Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. Cancer. 1998 Oct 15;83(8):1561-6.

Efstathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, Smith MR. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. J Clin Oncol. 2009 Jan 1;27(1):92-9.

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, et al. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: EORTC; 2001.

Fayers P, Bottomley A; EORTC Quality of Life Group; Quality of Life Unit. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur J Cancer. 2002 Mar;38 Suppl 4:S125-33.

FDA Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf. Accessed: 11 January 2017.

Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol. 2007 Mar;18(3):581-92.

Firmagon (degarelix for injection). Prescribing Information. Ferring Pharmaceuticals Inc., Parsippany, NJ, USA. Revised 07/2016. Available at: http://firmagon.com/. Accessed: 12 January 2017.

Foundation for Promotion of Cancer Research. Cancer Statistics in Japan-2012. December 2012.

Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA Cancer J Clin. 2001 Jan-Feb;51(1):15-36.

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.

Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, Swinburn P, Busschbach J. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013 Sep;22(7):1717-27.

Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006 Sep 20;24(27):4448-56.

Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, Jensen JK, Olesen TK, Schröder FH. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int. 2008 Dec;102(11):1531-8.

Klotz L, O'Callaghan C, Ding K, Toren P, Dearnaley D, Higano CS, Horwitz E, Malone S, Goldenberg L, Gospodarowicz M, Crook JM. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. J Clin Oncol. 2015 Apr 1;33(10):1151-6.

Kreis W. Current chemotherapy and future directions in research for the treatment of advanced hormone-refractory prostate cancer. Cancer Invest. 1995;13(3):296-312.

Lachin J. Biostatistical Methods: The Assessment of Relative Risks. 2nd ed. Balding D, Cressie N, Fitzmaurice G, Johnstone I, Molenberghs G, Scott D, et al., editors: John Wiley & Sons, Inc.; 2010.

Limonata P, Montagnani Marelli M, Moretti RM. LHRH analogues as anticancer agents: pituitary and extrapituitary sites of action. Expert Opin Investig Drugs. 2001 Apr;10(4):709-20.

Loblaw DA, Mendelson DS, Talcott JA, Virgo KS, Somerfield MR, Ben-Josef E, Middleton R, Porterfield H, Sharp SA, Smith TJ, Taplin ME, Vogelzang NJ, Wade JL Jr, Bennett CL, Scher HI; American Society of Clinical Oncology. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive

metastatic, recurrent, or progressive prostate cancer. J Clin Oncol. 2004 Jul 15;22(14):2927-41.

Lopez AM, Pena MA, Hernandez R, Val F, Martin B, Riancho JA. Fracture risk in patients with prostate cancer on androgen deprivation therapy. Osteoporos Int. 2005 Jun;16(6):707-11.

Lupron Depot. Prescribing Information. AbbVie Inc., North Chicago, IL, USA. Revised 6/2016. Available at: http://www.lupron.com/prescribing-information.aspx. Accessed: 12 January 2017.

Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. J Urol. 2002 Sep;168(3):1005-7.

Prostap 3 DCS. Summary of Product Characteristics, Section 4.8. Takeda UK Ltd. Revised 16/03/2016. Available at: https://www.medicines.org.uk/emc/medicine/24680. Accessed: 12 January 2017.

Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS; Urologic Diseases in America Project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer. 2007 Oct 1;110(7):1493-500.

Schally AV, Coy DH, Arimura A. LH-RH agonists and antagonists. Int J Gynaecol Obstet. 1980;18(5):318-24.

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, Antonarakis ES, Beer TM, Carducci MA, Chi KN, Corn PG, de Bono JS, Dreicer R, George DJ, Heath EI, Hussain M, Kelly WK, Liu G, Logothetis C, Nanus D, Stein MN, Rathkopf DE, Slovin SF, Ryan CJ, Sartor O, Small EJ, Smith MR, Sternberg CN, Taplin ME, Wilding G, Nelson PS, Schwartz LH, Halabi S, Kantoff PW, Armstrong AJ; Prostate Cancer Clinical Trials Working Group. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016 Apr 20;34(12):1402-18.

Shore ND. Experience with degarelix in the treatment of prostate cancer. Ther Adv Urol. 2013 Feb;5(1):11-24.

Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014 Jan-Feb;64(1):9-29.

Spry NA, Kristjanson L, Hooton B, Hayden L, Neerhut G, Gurney H, Corica T, Korbel E, Weinstein S, McCaul K. Adverse effects to quality of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer. Eur J Cancer. 2006 May;42(8):1083-92.

Tolis G, Ackman D, Stellos A, Mehta A, Labrie F, Fazekas AT, Comaru-Schally AM, Schally AV. Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. Proc Natl Acad Sci U S A. 1982 Mar;79(5):1658-62.

Tombal B, Miller K, Boccon-Gibod L, Schröder F, Shore N, Crawford ED, Moul J, Jensen JK, Kold Olesen T, Persson BE. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus

leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol. 2010 May;57(5):836-42.

Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst. 2007 Oct 17;99(20):1516-24.

Waxman J, Man A, Hendry WF, Whitfield HN, Besser GM, Tiptaft RC, Paris AM, Oliver RT. Importance of early tumour exacerbation in patients treated with long acting analogues of gonadotrophin releasing hormone for advanced prostatic cancer. Br Med J (Clin Res Ed). 1985 Nov 16;291(6506):1387-8.

APPENDICES

Appendix 1. Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Note: Adapted from Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

Appendix 2. EuroQol EQ-5D-5L Questionnaire

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

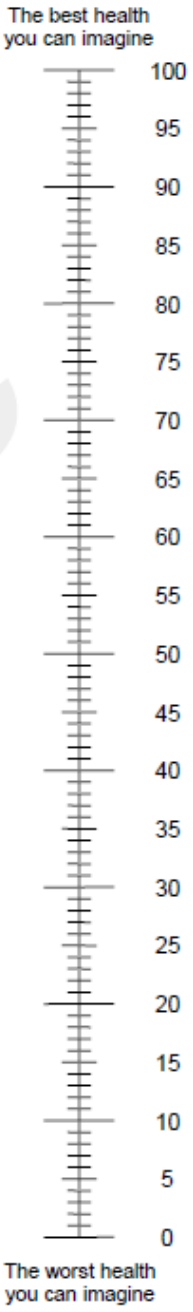
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 3. Quality of Life Questionnaire: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Today's date (Day, Month, Year): 31 ⌊3⌋⌊1⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4. Quality of Life Questionnaire: EORTC QLQ-PR25

ENGLISH

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid: Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

ENGLISH

During the last 4 weeks:	Not at all	A little	Quite a bit	Very much
47. Has weight **loss** been a problem for you?	1	2	3	4
48. Has weight **gain** been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS:

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

Appendix 5. Adverse Event Severity Grading

When assessing adverse events, refer to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, June 14, 2010 (available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). A copy of the National Cancer Institute CTCAE table will be provided in the investigator site file.

The National Cancer Institute CTCAE is a descriptive terminology that can be utilized for adverse event reporting. A grading (severity) scale is provided for each adverse event term.

Components and Organization of the National Cancer Institute CTCAE

- System Organ Class (SOC). SOC, the highest level of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy, is identified by anatomical or physiological system, etiology, or purpose (eg, SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, adverse events are listed and accompanied by descriptions of severity (grade).
- CTAE Terms. Each CTCAE term is a MedDRA LLT (Lowest Level Term).
- Definitions. A brief definition is provided to clarify the meaning of each adverse event term.
- Grades. Grade refers to the severity of the adverse event. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each adverse event based on this general guideline:
    - Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
    - Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
    - Grade 4 Life-threatening consequences; urgent intervention indicated; and
    - Grade 5 Death related to adverse event.

      A semi-colon indicates “or” within the description of the grade. A single dash (-) indicates a grade is not available. Not all grades are appropriate for all adverse events. Therefore, some adverse events are listed with fewer than 5 options for grade selection.
- Grade 5. Grade 5 (Death) is not appropriate for some adverse events and therefore is not an option.

Appendix 6. Guidelines for Elevations in Hepatic Enzymes

Study drug treatment should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline. For this purpose, local labs can be used. However, duplicate samples should be taken for central analysis.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld, even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests[a,b]
If AST or ALT ≥ 3 x ULN **and** total bilirubin > 2 x ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 x ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions

b. Local labs can be used. However, duplicate samples should be taken for central analysis.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

- Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever);
- Prior and concurrent disease or illnesses;
- Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents;
- Prior and concurrent use of alcohol, recreational drugs, and special diets;
- Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms;
- Physical examination.

Recommended tests:

Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist.

- Repeat liver tests as per Appendix Table 1[a];
- Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests;
- Complete blood count with differential to assess for eosinophilia;
- Serum acetaminophen (paracetamol) concentration;
- Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus;
- Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc;
- Serology for celiac disease;
- Appropriate liver imaging; and
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

Abbreviations: INR, international normalized ratio

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

CLINICAL STUDY PROTOCOL

Study Title:	HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3201
Indication:	Advanced Prostate Cancer
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
IND Number:	118736
EudraCT Number:	2017-000160-15
Version/Effective Date:	Original: 13 January 2017 Amendment 1: 02 January 2018 Amendment 2: 18 January 2018 Amendment 3: 23 October 2018
Study Medical Monitor:	PPD

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer

Protocol Number: MVT-601-3201

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

23 Oct 2018

Date

23 OCT 2018

Date

~~23 OCT 2018~~ PPD 23 OCT 2018

Date

23-OCT-2018

Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	**Signature**
Date	**Site**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
3-M	3-month
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
$AUC_{0-\tau}$	area under the concentration-time curve from time 0 to the end of the dosing interval
AV	atrioventricular
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DHT	dihydrotestosterone
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation of Research and Treatment of Cancer
EOT	end of treatment
EuroQol EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Questionnaire
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HbA1c	hemoglobin A1c
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
ICH	International Conference on Harmonization
ID	identification
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat (population)
IWRS	interactive voice/web recognition system
LH	luteinizing hormone
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

Term	Explanation
NOAEL	no-observed-adverse-effect-level
NYHA	New York Heart Association
Obs	observed
PK	pharmacokinetics
PLD	phospholipidosis
PSA	prostate-specific antigen
Q12W	once every 12 weeks
Q4W	once every 4 weeks
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QTc corrected using Fridericia's formula
SHBG	sex hormone binding globulin
TCR	time to castration-resistance
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States

1. PROTOCOL SYNOPSIS

Study Title	HERO: A Multinational Phase 3, Randomized, Open-label, Parallel-group Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer
Protocol Number	MVT-601-3201
Location	Multinational, including North and South America, Europe, and Asia-Pacific
Study Centers	Approximately 200 sites
Study phase	Phase 3
Target Population	Men aged 18 or older diagnosed with androgen-sensitive advanced prostate cancer who are candidates for at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer and who are not candidates for surgical therapy. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy.
Number of Patients Planned	A total of approximately 1100 patients will be enrolled, including approximately 390 patients with metastatic advanced prostate cancer to support the analysis of the secondary endpoint of time to castration-resistance (TCR), and 138 Chinese patients (enrolled in China and Taiwan) to support registration in China. • After the first 915 patients are enrolled, enrollment in China will continue for metastatic and non-metastatic patients until the target number of Chinese patients is reached (138). In the rest of the world, only metastatic patients will continue to be enrolled until approximately 390 metastatic patients are accrued. • The primary analysis of efficacy and safety will be conducted after the first 915 patients, enrolled in all regions, have completed study treatment and will include metastatic and non-metastatic patients with advanced prostate cancer. • Analysis of the secondary endpoint of TCR will be conducted when all metastatic patients have completed study treatment. • An analysis will be conducted when all Chinese patients have completed study treatment.
Study Objectives	Primary: • To evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) in men with androgen-sensitive advanced prostate cancer. Secondary: • To evaluate the time course and change in serum testosterone during treatment with relugolix; • To evaluate the time course and magnitude of prostate-specific antigen (PSA) reduction during treatment with relugolix; • To evaluate testosterone recovery following discontinuation of relugolix; • To evaluate quality of life using validated patient-reported outcome instruments;

	• To evaluate the safety of relugolix 120 mg once daily in men with androgen-sensitive advanced prostate cancer; • To evaluate the effect of relugolix and leuprolide acetate on endocrine pharmacodynamic parameters; • To collect relugolix plasma concentration data to further evaluate relugolix population pharmacokinetics (PK) and the relationship between relugolix exposure and serum testosterone; • To characterize the relugolix plasma PK parameters in a subset of patients from China and Japan. • *For patients with metastatic advanced prostate cancer (approximately 390 patients)*: To evaluate the time course and magnitude of PSA progression and development of castration-resistant prostate cancer during treatment with relugolix. • *For all enrolled patients (approximately 1100 patients)*: To evaluate the time course and magnitude of PSA progression and development of castration-resistant prostate cancer during treatment with relugolix. Exploratory: • To explore the overall survival of patients treated with relugolix; and • To explore the contribution of genetic variance on drug response.

Study Design

The HERO study is a phase 3 multinational randomized, open-label, parallel-group study to evaluate the safety and efficacy of relugolix in patients with androgen-sensitive advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy. Relugolix is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist that lowers testosterone by inhibiting pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Relugolix 120 mg orally once daily or leuprolide acetate depot suspension, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China), every 3-months (3-M) will be administered to patients with prostate cancer who require androgen deprivation therapy. This study will evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) for 48 weeks in patients with androgen-sensitive advanced prostate cancer.

To be eligible for the study, a patient must be, in the opinion of the investigator, a candidate for at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer and must not be a candidate for surgical therapy. Eligible patients include those with evidence of biochemical relapse (rising PSA) following local primary intervention with curative intent, newly diagnosed metastatic disease (excluding metastases to the brain), and/or advanced localized disease. Patients may receive radiotherapy, cryotherapy or high frequency ultrasound no sooner than 2 months after initiation of androgen deprivation therapy. Patients may be included if they have not previously received androgen deprivation therapy for more than 18 months, and if the androgen deprivation therapy was completed at least 3 months prior to the baseline visit. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy, are excluded, as are patients receiving

androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy. Baseline serum testosterone must be ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L) to be enrolled.

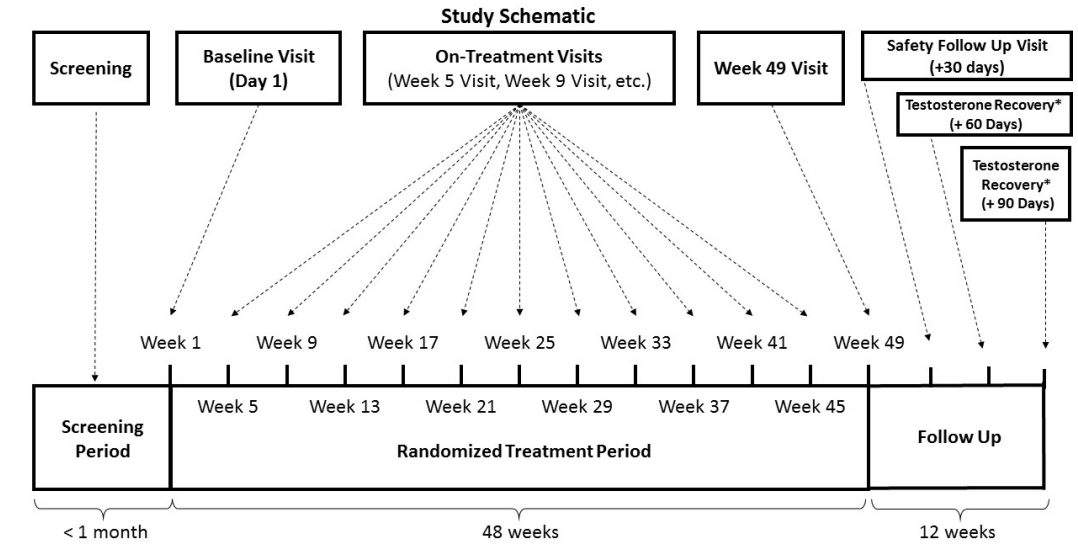
Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg once daily following a loading dose of 360 mg on Day 1 or 3-M depot of leuprolide acetate 22.5 mg (or 11.25 mg in Japan, Taiwan, and China). After randomization, patients in the leuprolide acetate arm may receive an antiandrogen for the first 4 weeks, or longer if indicated, in the opinion of the investigator. Randomization will be stratified by geographic region, presence of metastatic disease (metastases in regional lymph node[s] are considered N1 and will, therefore, be stratified as non-metastatic), and age for the initial 915 enrolled from all regions or among the approximately 138 Chinese patients.

A total of approximately 1100 patients from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region are planned to be enrolled in this study. Included in the 1100 enrolled patients will be approximately 390 patients with metastatic advanced prostate cancer to support the analysis of the secondary endpoint of TCR (these patients will be stratified by geographic region and age only), and 138 Chinese patients (enrolled in China and Taiwan) to support registration in China.

Approximately 138 Chinese patients will be enrolled (in China and Taiwan). Similar to the initial 915 patients enrolled in the HERO study, these Chinese patients will include patients with metastatic and non-metastatic advanced prostate cancer.

The study includes a Screening Period of up to 28 days, a Treatment Period of 48 weeks, and a Follow-up Period of up to 90 days. Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed. Eligible patients will receive study treatment for 48 weeks. During that time, testosterone and PSA will be assessed monthly and patient-reported outcomes (European Organisation of Research and Treatment of Cancer [EORTC] QLQ-C30, European Quality of Life 5-Dimesion 5-Level questionnaire [EuroQol EQ-5D-5L]) will be assessed approximately every 3 months during the Treatment Period and more frequently during the Follow-up Period. Additional serum endocrine evaluations will include: LH, FSH, dihydrotestosterone, and sex hormone binding globulin. Relugolix PK samples will be collected throughout the study. Full PK profiles will be determined in a subset of patients in China and Japan. Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECG), and visual acuity tests.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]), should be encouraged to remain on study and, if indicated, may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide after the confirmation of PSA progression. For patients requiring other systemic antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.



Inclusion/Exclusion Criteria

Inclusion Criteria

All of the following inclusion criteria must have been met prior to randomization unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a male aged 18 years or older on the day of signing and dating the informed consent form;
3. Has histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate;
4. Is a candidate for, in the opinion of the investigator, at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer with one of the following clinical disease state presentations:
   a. Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, such as surgery, radiation therapy, cryotherapy, or high-frequency ultrasound and not a candidate for salvage treatment by surgery; or
   b. Newly diagnosed androgen-sensitive metastatic disease; or
   c. Advanced localized disease unlikely to be cured by local primary intervention with either surgery or radiation with curative intent;

   Note: Radiotherapy, cryotherapy, or high frequency ultrasound are allowed after 2 months of androgen deprivation therapy. Prior palliative radiation to sites other than the prostate bed is permitted.

   Note: Once 915 patients are enrolled worldwide, only patients with metastatic advanced prostate cancer will be eligible for the study in all regions except China, where both metastatic and non-metastatic patients will continue to be enrolled.
5. Has a serum testosterone at the Screening visit of ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L);

6. Has a serum PSA concentration at the Screening visit of > 2.0 ng/mL (2.0 µg/L), or, when applicable, post radical prostatectomy of > 0.2 ng/mL (0.2 µg/L) or post radiotherapy, cryotherapy, or high frequency ultrasound > 2.0 ng/mL (2.0 µg/L) above the post interventional nadir;

   Note: If patient has had a radical prostatectomy then PSA must be > 0.2 ng/mL (0.2 µg/L) irrespective of any other treatment the patient has had.

7. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at initial screening and at baseline (refer to Appendix 1);

8. Is a male patient who, even if surgically sterilized (ie, status post vasectomy):

   a. Agrees to use a male condom if having sex with a woman of childbearing potential or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or

   b. Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception;

9. Must agree not to donate sperm from first dose of study drug through 4 months after the last dose of study drug;

10. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

1. In the investigator's opinion, is likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating androgen deprivation therapy;

2. Previously received GnRH analog or other form of androgen deprivation therapy (estrogen or antiandrogen) for > 18 months total duration. If androgen deprivation therapy was received for ≤ 18 months total duration, then that therapy must have been completed at least 3 months prior to baseline. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot;

3. Previous systemic cytotoxic treatment for prostate cancer (eg, taxane-based regimen);

4. Metastases to brain per prior clinical evaluation;

5. *Removed;*

6. Scheduled for major surgery after baseline;

7. History of surgical castration;

8. Active malignancy beyond prostate cancer ***with the exception*** of any of the following:

   - Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ carcinoma of any type;
   - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for ≥ 2 years;
   - Any other cancer from which the subject has been disease-free for ≥ 5 years;

   The medical monitor should be contacted for any questions regarding this exclusion criterion;

9. Abnormal laboratory values at the Screening visit that suggest a clinically unstable underlying disease, or the following laboratory values:

a. Serum gamma-glutamyl transferase > 2.0 x upper limit of normal (ULN);

b. Serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > ULN;

c. Total bilirubin > ULN (unless secondary to Gilbert's syndrome or the pattern is consistent with a diagnosis of Gilbert's syndrome);

d. Serum creatinine > 2.0 mg/dL (176.8 µmol/L);

e. Platelets < 100 x 10^3/µL or history of bleeding disorder;

f. Hemoglobin < 10.0 g.dL (100 g/L);

g. Leukocytes (WBC) < 3 x 10^3/µL (3 GI/L); or

h. Absolute neutrophil count < 1.5 x 10^3/µL (1.5 GI/L);

10. Hemoglobin A1c (HbA1c) > 10% in patients previously diagnosed with diabetes mellitus. HbA1c > 8% in patients whose diabetes mellitus is previously undiagnosed. (Excluded patients may be rescreened after referral and evidence of improved control of their condition);

11. Has jaundice or known current active liver disease from any cause, including hepatitis A (hepatitis A virus immunoglobulin M [IgM] positive), hepatitis B (hepatitis B virus surface antigen [HBsAg] positive), or hepatitis C (hepatitis C virus [HCV] antibody positive, confirmed by HCV ribonucleic acid);

12. Known human immunodeficiency virus infection;

13. Any of the following within 6 months before Baseline Day 1:

    a. Myocardial infarction;

    b. Unstable angina;

    c. Unstable symptomatic ischemic heart disease;

    d. New York Heart Association (NYHA) class III or IV heart failure;

    e. Thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events);

    f. Any other significant cardiac condition (eg, pericardial effusion, restrictive cardiomyopathy, severe untreated valvular stenosis, or severe congenital heart disease);

14. The following ECG abnormalities are excluded:

    a. ECG evidence of acute ischemia;

    b. Q-wave infarction, unless identified 6 or more months before the Screening visit;

    c. QT interval corrected for heart rate (QTc) > 470 msec, measured by Fridericia's formula [QTcF = QT/(RR^0.33)]. If the QTc is prolonged in a patient with a pacemaker, the patient may be enrolled in the study if confirmed by the medical monitor; or

    d. Congenital long QT syndrome;

    e. Active conduction system abnormalities. Examples of active conduction system abnormalities include the following:

        - Mobitz II second degree heart block without a permanent pacemaker in place;
        - Third degree heart block without permanent pacemaker in place;

- Untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
- Clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes;
- Uncontrolled atrial fibrillation (patients with chronic stable atrial fibrillation on stable anticoagulant therapy or patients with stable cardiac rhythm controlled by a pacemaker are allowed);

The following exceptions are allowed: First degree atrioventricular (AV) block, second degree AV block Type 1 (Mobitz Type 1/Wenckebach type), or right bundle branch block.

15. Uncontrolled hypertension despite appropriate medical therapy (sitting blood pressure of greater than 160 mmHg systolic and/or 100 mmHg diastolic at 2 separate measurements no more than 45 minutes apart during the Screening visit). Patients may be re-screened after referral and further management of hypertension;
16. Hypotension, as indicated by systolic blood pressure < 84 mmHg on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming upright position;
17. Bradycardia as indicated by a heart rate of < 45 beats per minute on the ECG at the Screening or Baseline Day 1 visit;
18. Treatment with any investigational product within 28 days or 5 half-lives (whichever is longer);

    Exception: treatment for prostate cancer with any investigational products where the mechanism of action is testosterone lowering. In this circumstance, there must be a minimum 12-month treatment free interval;
19. *Removed*;
20. Previous treatment with relugolix in a clinical study;
21. Patient is a study site employee or is a primary family member (spouse, parent, child, or sibling) of a site employee involved in the conduct of the study;
22. Known gastrointestinal disease or procedure that could interfere with the oral absorption or tolerance of relugolix, including inability to swallow whole tablets or conditions that may interfere with absorption at the level of the small intestine. Examples of such conditions include but are not limited to Crohn's disease, gastric bypass, active peptic ulcer disease, and gastrectomy. The medical monitor should be contacted for any questions regarding this exclusion criterion;
23. Use or planned use of any medication listed in the prohibited medications table (see Section 5.10.1) without the appropriate washout period;
24. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
25. Has a prior (within 1 year of the Screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form [eCRF]);
26. Any other medical or psychiatric condition that, in the opinion of the investigator, would interfere with completion of treatment according to this protocol.
27. Weight ≥ 400 pounds (181 kg) or has a body mass index ≥ 50;

Dose and Route of Administration	Test Product Relugolix 120 mg tablet strength will be available as immediate-release film-coated tablets, and 1 tablet (120 mg) will be administered once daily following an oral loading dose of 360 mg (three 120-mg tablets) on Day 1. These tablets will be presented in 45-tablet bottles and dispensed to patients every 4 weeks at scheduled study visits. All protocol-specific inclusion criteria and none of the exclusion criteria must be met and documented prior to study drug administration. Study drug will be dispensed only to eligible patients who are under the supervision of the investigator or identified subinvestigator(s). Reference Product Leuprolide acetate, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China), 3-M depot will be administered per the approved dose and method of dosing in the region where the patient is enrolled. Leuprolide acetate 3-M depot injection will be administered on Day 1 (with an antiandrogen of choice, if indicated according to the investigator, for the first 4 weeks or longer), then at 12-week intervals thereafter for 48 weeks. Preparation of the depot injection and administration should follow the instructions provided by the manufacturer.
Duration of Treatment	The duration of treatment will be 48 weeks. The last dose of leuprolide acetate 3-M depot will be administered at the Week 37 visit.
Criteria for Evaluation	The following treatment arms will be evaluated after 48 weeks of study treatment: • Arm A: Oral relugolix 120 mg once daily following a loading dose of 360 mg (three 120-mg tablets) on Day 1. • Arm B: Leuprolide acetate 3-M depot injection, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China).
	Primary Endpoint *For the first 915 patients randomized*: • Sustained castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337).
	Secondary Endpoints *For the first 915 patients randomized*: • Describe effects on serum testosterone: o Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4, prior to dosing on Week 3 Day 1; o Profound castration rate, defined as the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) while on study treatment from Week 25 Day 1 through Week 49 Day 1;

	○ Time to testosterone recovery in approximately 100 patients randomized to relugolix and approximately 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of leuprolide acetate 3-M depot); • Describe effects on PSA: ○ Proportion of patients with confirmed PSA response by Prostate Cancer Clinical Trials Working Group 3 guidelines at the Week 3 and Week 5 visits [Scher, 2016]; ○ Proportion of patients with PSA concentration < 0.2 ng/mL (0.2 µg/L) at the Week 3 and Week 5 visits; • Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable during the Follow-up and/or at End of Treatment visits; • Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as the EuroQol EQ-5D-5L questionnaire, at regular intervals during treatment, and as applicable during the Follow-up visits; • Incidence of adverse events; • Incidence of abnormalities in clinical laboratory data; • Endocrine marker effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for: ○ LH at the Day 4, Week 5, Week 25, and Week 49 visits; ○ FSH at the Day 4, Week 5, Week 25, and Week 49 visits; ○ Dihydrotestosterone at the Week 5, Week 25, and Week 49 visits; and ○ Sex hormone binding globulin at the Week 5, Week 25, and Week 49 visits; • Predose relugolix plasma concentrations; • Single and repeat-dose plasma relugolix PK parameters such as maximum plasma concentration (C_{max}), area under the concentration-time curve from time 0 to the end of the dosing interval ($AUC_{0-\tau}$), and time to maximum plasma concentration (t_{max}) in a subset of patients from China and Japan during the Day 1 visit; • Time to PSA progression.

	For patients with metastatic advanced prostate cancer (approximately 390 patients): • Time to castration-resistant (TCR) during the 48-week of treatment; *For all enrolled patients (approximately 1100 patients):* • TCR during the 48-week treatment *Exploratory Endpoints* • Overall survival defined as time from randomization to date of death prior to data cutoff date; and • The presence of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix. These will be evaluated in a subset of patients.

Statistical Methods

A statistical analysis plan will describe the detailed statistical methods and analyses for this study. The statistical analysis plan will be prepared and finalized before database lock for the primary analysis.

There will be two analyses for the study, a primary analysis and a final analysis. The primary analysis of efficacy and safety will occur after approximately the first 915 patients have been randomized to the study (ITT population) and have had the opportunity to be evaluated for 48 weeks and complete the 30-day safety follow-up visit.

The final analysis will occur after approximately 390 metastatic patients have been randomized to the study and have had the opportunity to be evaluated for 48 weeks of study treatment and complete the 30-day safety follow-up visit or discontinued early.

TCR in the subgroup of metastatic patients and the extended ITT population (approximately 1100 patients) will be analyzed only at the time of the final analysis.

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) population defined as all randomized patients who have taken at least one dose of study treatment. Randomization will be stratified by geographic region (North and South America versus Europe versus Asia and Rest of World), presence of metastatic disease (metastases in regional lymph node[s] are considered N1 and will, therefore, be stratified as non-metastatic) on baseline imaging (yes versus no), and age (≤ 75 years old versus > 75 years old). The 2-sided type I error rate for this study is 0.05.

After the initial 915 patients have been enrolled, only patients with metastatic advanced prostate cancer from other regions will continue to be enrolled (these patients will be stratified by geographic region and age only), except for China, where both metastatic and non-metastatic patients will continue to be enrolled (these patients will continue to be stratified using all of the stratification factors).

Primary Efficacy Endpoint:

The primary efficacy endpoint is the sustained castration rate defined as the cumulative probability of achieving testosterone suppression to castrate levels of ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). This probability will be estimated for each treatment group using the Kaplan-Meier method with the confidence interval calculated using the exponential Greenwood formula via log-log transformation of the survival function. Patients who discontinue treatment prior to observing a testosterone level > 50 ng/dL (1.7 nmol/L) will be censored at the last testosterone assessment prior to discontinuation. Detailed censoring rules will be prespecified in the statistical analysis plan.

There are 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit:

- Evaluation Criterion 1: to determine whether the sustained castration rate for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression to castrate levels in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion.
- Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot as assessed by the cumulative probability of sustained testosterone suppression to castrate levels. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression to castrate levels between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.

The 2-sided type I error rate will be 0.05 for each individual evaluation criterion.

Secondary Efficacy Endpoints:

1. Castration rate: the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4, and prior to dosing on Week 3 Day 1;
2. Profound castration rate: the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) from Week 25 through Week 49;
3. PSA response rate: proportion of patients with a ≥ 50% decrease in PSA from baseline at Week 3 and confirmed at Week 5;
4. Undetectable PSA rate: proportion of patients with PSA concentration < 0.2 ng/mL (0.2 µg/L) at the Week 3 and Week 5 visits;
5. Time to testosterone recovery in approximately 100 relugolix-treated and approximately 50 leuprolide acetate-treated patients who complete 48 weeks of treatment and do not start alternative androgen deprivation therapy within 12 weeks after the last dose of relugolix or within 24 weeks following the last received injection of leuprolide acetate. Kaplan-Meier methods will be used to describe survival distributions;
6. Quality of Life: absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable at the Follow-up and/or End-of-Study visits will be presented. Additionally, absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as EQ-5D-5L, at regular intervals during treatment, and as applicable during the Follow-up visits will be presented. Change from baseline will be analyzed using mixed-model repeated measures methodology;
7. Time to PSA progression: defined per Prostate Cancer Clinical Trials Working Group 3 guidelines as the first increase in PSA of 25% or greater and 2 ng/mL or greater above the nadir with confirmation by a second PSA measurement at least 3 weeks later. For patients without declining PSA from baseline, PSA increase of 25% or greater and 2 ng/mL from baseline beyond 12 weeks will be considered PSA progression.
8. TCR in the subgroup of metastatic patients and the extended ITT population will only be evaluated at the time of final analysis, when approximately 1100 patients (reaching at least 390 metastatic patients) have been randomized to the study and have had the opportunity to be evaluated for 48 weeks of study treatment and complete the 30-day safety follow-up or discontinued early. TCR is defined as the time from the date of first dose to the date of PSA progression while castrated or death due to any reason, whichever occurs earlier. TCR will be analyzed using the Kaplan-Meier method. Treatment comparison with hazard ratios will be performed using Cox proportional hazards model.

Exploratory Endpoints:

1. Overall survival: Overall survival defined as time from randomization to date of death prior to data cutoff date. Kaplan-Meier methods will be used to describe survival distributions;
2. The effect of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or drug metabolizing enzymes and transporter proteins on the efficacy and safety of relugolix will be described in a separate statistical analysis plan.

The methods and procedures needed to maintain a study-wide 2-sided type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

Pharmacokinetics

Relugolix plasma concentrations will be summarized and described using population PK methods. Plasma PK parameters in a subset of patients from China and Japan will be determined using noncompartmental methods.

Safety

Safety assessments, including adverse events, vital signs, clinical laboratory tests, and ECGs, will be summarized for the treatment-emergent period. The treatment-emergent period is defined as the time from first dose of study drug through 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last dose of leuprolide acetate. Safety analyses will be based on all randomized patients who receive any amount of study drug (Safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher-level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive rather than inferential statistics will be used. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of baseline versus post baseline results will be produced.

An independent Data and Safety Monitoring Board will monitor all available safety data on a periodic basis. The roles and responsibilities of the Data and Safety Monitoring Board will be described in detail in a separate charter.

Sample Size

To calculate the sample size required for the primary efficacy endpoint of this study, the following assumptions have been made:

- True probabilities of sustained castration rates are 94% and 96% for relugolix and leuprolide acetate, respectively;
- 2:1 randomization ratio (relugolix:leuprolide acetate);
- Dropout rate of 15%.

For Evaluation Criterion 1, 610 patients in the relugolix group will provide approximately 90% power to rule out a fixed probability of sustained testosterone suppression of ≤ 90% at a 2-sided type I error rate of 0.05.

For Evaluation Criterion 2, with the non-inferiority margin of -10% and a 2-sided type I error rate of 0.05, a total of approximately 915 patients (610 relugolix, 305 leuprolide acetate) will yield at least 99% power in declaring the non-inferiority of relugolix compared to leuprolide acetate.

The primary analysis will be performed separately for individual evaluation criterion using data collected through 48 weeks after enrollment of approximately 915 patients.

Approximately 915 patients will be randomized in order to fulfill the regulatory requirements of all participating countries included in the primary efficacy endpoint of this study.

The study is also powered for the secondary endpoint of TCR in the high-risk subgroup of metastatic patients. Approximately 107 confirmed castration-resistance events (PSA progressions while castrated or deaths due to any cause) will need to be observed (or approximately 390 metastatic patients will need to be enrolled) to detect a hazard ratio of 0.55 (relugolix versus leuprolide acetate) with 85% power with a two-sided type I error of 5%, assuming a castration-resistant event-free rate of 60% at 48 weeks for the control arm, 18-month enrollment period, 12 months of additional follow-up, and a 15% dropout rate.

With a total of approximately 1100 patients (metastatic or non-metastatic) randomized into the study including approximately 138 Chinese patients, it is anticipated to observe approximately 149 confirmed castration-resistant events (PSA progression while castrated or deaths due to any cause). Assuming an 18-month enrollment period, 12 months of additional follow-up, and a 10% dropout rate, the study will provide approximately 85% power to detect a hazard ratio of 0.6 (relugolix versus leuprolide acetate) with a two-sided type I error of 5%.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3201

Period	Screening Visit	Treatment Period Visits													Follow-up[a,c]		
															Safety[b]	Testosterone Recovery	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2[q]**	**Wk 3**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17 and 21**	**Wk 25**	**Wk 29 and 33**	**Wk 37**	**Wk 41 and 45**	**Wk 49[e]**	**Un-scheduled**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**		**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**	**±2 days**				**± 7 days**										**± 7 days**		
Informed Consent[f]	X																	
Inclusion/ Exclusion Criteria	X	X																
Study Drug Dispensation: Relugolix		X				X	X	X	X	X	X	X	X		X[r]			
Study Drug Administration: Relugolix Once Daily		X	X Patients will receive a single loading dose of oral relugolix 360 mg on Day 1 in the clinic; Starting on Day 2, patients will take oral relugolix 120 mg once daily												X[r]			
Study Drug Administration: Leuprolide Acetate 3-M Depot		X						X		X		X			X[r]			
Phone call prior to visit and study drug accountability[d]						X	X	X	X	X	X	X	X	X	X[r]			
Demographics	X																	
Medical History (including detailed prostate cancer history)	X	X																
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X	X
Weight, BMI	X	X						X		X				X	X[r]	X		
Height	X														X[r]			
12-lead ECG[g]	X	X				X		X		X				X	X[r]	X		

Period	Screening Visit	Treatment Period Visits														Follow-up[a,c]		
																Safety[b]	Testosterone Recovery	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2[q]**	**Wk 3**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17 and 21**	**Wk 25**	**Wk 29 and 33**	**Wk 37**	**Wk 41 and 45**	**Wk 49[e]**	**Un-scheduled**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**		**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**	**±2 days**				**± 7 days**										**± 7 days**		
ECOG Performance Assessment	X	X								X				X	X[r]	X		
Complete Physical Exam and Visual Acuity[h]	X									X				X	X[r]			
Symptom Based Physical Exam		X				X	X	X	X		X	X	X		X[r]	X	X	X
Abdominopelvic CT or MRI and Bone Scan[i]	X														X[r]			
EuroQol EQ-5D-5L Health Questionnaire		X				X		X		X		X		X	X[r]	X	X	X
EORTC-QLQ-PR25 and EORTC-QLQ-C30 Quality of Life Questionnaires		X				X		X		X		X		X	X[r]	X	X	X
Adverse Events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X	X
Hematology	X	X						X		X		X		X	X[r]	X		
Chemistry	X	X				X		X		X		X		X	X[r]	X		
Lipid & HbA1c[k]	X									X				X	X[r]	X		
PSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X	X
Serum Testosterone	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[r]	X	X	X
LH/FSH		X	X			X				X				X	X[r]	X	X	X
SHBG/DHT		X				X				X				X	X[r]			X

Period	Screening Visit	Treatment Period Visits														Follow-up[a,c]		
																Safety[b]	Testosterone Recovery	
Visit Name	**Screening**	**Baseline Day 1**	**Day 4**	**Wk 2[q]**	**Wk 3**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17 and 21**	**Wk 25**	**Wk 29 and 33**	**Wk 37**	**Wk 41 and 45**	**Wk 49[e]**	**Un-scheduled**	**30-Day**	**60-Day**	**90-Day**
Study Day	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**57**	**85**	**113 and 141**	**169**	**197 and 225**	**253**	**281 and 309**	**337**		**EOT + 30 days**	**EOT + 60 days**	**EOT + 90 days**
Visit Window	**Not applicable**	**±2 days**				**± 7 days**										**± 7 days**		
Blood Sample for Relugolix PK[m,n]		X[m,n]	X[n]	X[n]		X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[r]			
Blood Sample for DNA[o]		X													X[r]			
Health Status Survey[p]														X	X[r]			

Abbreviations: 3-M, 3-month; BMI, body mass index; CT, computed tomography; DHT, dihydrotestosterone; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; EuroQol EQ-5D-5L, European Quality of Life 5-Dimension 5-Level; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; LH, luteinizing hormone; MRI, magnetic resonance imaging; PK, pharmacokinetics; PSA, prostate-specific antigen; SHBG, sex hormone binding globulin

a. The study day in which the Follow-up visit occurs is not specified in the table because these visits occur relative to when the patient takes his last dose of study drug. The End of Treatment (EOT) is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.
b. May occur earlier for patients who are starting alternative androgen deprivation therapy, or do not complete 12 weeks of study treatment. Adverse events, serious adverse events, and concomitant medications should continue to be collected and recorded through 30 days after the End of Treatment. All other study procedures should be completed before the start of alternative androgen deprivation therapy.
c. Patients who have started alternative androgen deprivation therapy will not participate in the 60- and 90-day Follow-up visits. For approximately 100 patients receiving relugolix and approximately 50 patients receiving leuprolide acetate who complete 48 weeks of study drug treatment and, in the opinion of the investigator, can remain off androgen deprivation therapy for 90 days will be included in the testosterone recovery 60- and 90-day Follow-up visits.
d. For patients assigned to the relugolix treatment arm, the patient should be called 7 days before their next visit to check on compliance with their study medication. Study drug accountability will be conducted at visits and results will be recorded as the primary source of study drug accountability.
e. If patient terminates early from study treatment, the patient should be asked to come in as soon as possible and complete this visit.
f. The informed consent form must be signed before any study-mandated procedures are performed.
g. 12-lead ECGs should be read locally by a qualified physician.
h. A complete physical examination should be performed. Visual acuity will be evaluated by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment. Patients whose presenting visual acuity score is 90 or lower at the screening visit should be encouraged to obtain a diagnostic evaluation from an eye care provider (ie, an ophthalmologist or an optometrist). Any findings (ie, diagnoses) from the eye examination should be recorded as medical history. Patients whose presenting visual acuity score at Week 25, Week 49, or Early Termination has decreased by 10 or more points from the screening visit should be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.

i. An abdominopelvic CT or MRI and a bone scan should be performed and read locally to determine the presence of metastatic disease within 60 days prior to randomization. However, if CT or MRI demonstrates presence of metastatic disease, a bone scan is not required. If metastatic disease is not present on CT or MRI, then a bone scan is also required. With the exception of China, which will enroll patients with metastatic and non-metastatic advanced prostate cancer, once 915 patients are enrolled, only patients with metastatic advanced prostate cancer will be eligible for the study, and metastatic disease must be confirmed on either abdominopelvic CT/MRI or bone scan.
j. Collect serious adverse event information from the time of signed informed consent through the Safety Follow-up Visit, which is through 30 days after the last dose of relugolix or 12 weeks and 30 days after the last injection of leuprolide acetate, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit (or from the time of signed informed consent if event was related to a screening study procedure through approximately 30 days after the last dose of relugolix or 12 weeks and 30 days after the last injection of leuprolide acetate, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first.
k. Blood samples must be obtained fasting; nothing to eat or drink (other than water) for at least 9 hours prior to obtaining the sample.
l. All testosterone samples obtained from Week 5 and beyond are to be collected during a ± 7-day window.
m. Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose, approximately 24 hours after the previous dose. Patients may be dosed in the clinic at these visits, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing.
n. A subset of patients from China and Japan will have additional samples collected predose, and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Day 1 and Week 2 visits. Patients will be dosed in the clinic at these visits. The dose will be administered at least 2 hours after food; food should be withheld for 1 hour after dosing. A predose sample (approximately 24 hours after the previous dose) also will be collected at the Day 4 visit. Patients may be dosed in the clinic at the Day 4 visit, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing.
o. The blood sample for DNA should be collected at the Baseline Day 1 visit but may be collected at any visit if it is missed at that visit.
p. During the final weeks prior to database lock, sites will be asked to contact all study participants or their immediate family regarding the current health status of previously enrolled/completed study patients.
q. Week 2 visit will only occur for patients who are part of the Japan or China subset for PK analysis.
r. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.

2. INTRODUCTION

2.1. Prostate Cancer

Prostate cancer is the most prevalent form of cancer in men and the second leading cause of death due to cancer in men in the US [Greenlee, 2001] and Europe [Ferlay, 2012]. The median age of diagnosis is 70 years, and diagnosis before the age of 40 years is rare [Cersosimo, 1996]. In Japanese men, prostate cancer was the fourth leading cancer diagnosis in 2007 [Foundation for Promotion of Cancer Research, 2012]. The incidence of invasive prostate cancer increases with age; a clear increase is seen among men aged 60 years or older [Siegel, 2014].

If prostate cancer is diagnosed at a stage where it is confined to the prostate gland and immediate surroundings, it is generally treated by surgical removal of the prostate gland, or prostatectomy, or with radiation. Often, these procedures are successful in curing men of their disease. Men whose disease progresses after prostatectomy or radiation are said to have advanced prostate cancer. Advanced prostate cancer is defined as either: PSA biochemical relapse following primary surgical or radiation therapy of curative intent; newly diagnosed metastatic prostate cancer; or advanced localized disease for which immediate radiation or surgical therapy is not indicated. The cure rate following surgery, depending on the stage of the cancer, is about 70% overall and, following radiation, about 50% to 60%.

Approximately 25% to 30% of men will, therefore, progress to advanced disease, excluding those with metastatic disease at the time of diagnosis. Androgens, such as testosterone and its more potent metabolite dihydrotestosterone, are strong tumor promoters for prostate cancer [Bosland, 2014]. Through the androgen receptor, they synergistically augment the effect of other tumor promoters or carcinogens. Although prostate cancer is driven by presumed mutations in other tumor promoting pathways and/or by translocations leading to aberrant activation of the androgen receptor pathway, most early-stage prostate cancer cells remain either sensitive to or dependent upon circulating androgens. Thus, for more than 60 years, androgen deprivation therapy with surgical or medical castration has been the foundational therapy for either advanced inoperable or metastatic cancer. Increasingly, androgen deprivation therapy is used earlier as a neoadjuvant/adjuvant treatment to radiation therapy or for biochemical or clinical relapse after local therapies of curative or palliative intent. More than 80% of men with progressive or advanced disease initially respond to androgen deprivation therapy with varying degrees of tumor regression or stabilization [Kreis, 1995]. The duration and depth of response to androgen deprivation therapy is presumably dependent on the underlying tumor biology and burden. Thus, patients with metastases respond for an average of 2 years before any biochemical evidence of castration-resistance occurs. By contrast, patients with biochemical-only evidence of progressive disease may respond to androgen deprivation therapy for 5 years or more [Klotz, 2015].

Currently, most patients in developed countries receive medical rather than surgical castration. GnRH (or LH-releasing hormone) agonists (ie, long-acting leuprolide acetate depot injections) are the current mainstay of medical castration, causing long-term desensitization and down regulation of the hypothalamic-pituitary gonadal axis. One disadvantage of the agonist form of GnRH is the initial stimulation of the axis lasting 1 to 3 weeks that occurs prior to desensitization. This results in a rise in LH and testosterone levels and an increase in clinical symptoms. In addition, at the time of repeat injection of GnRH agonist depot, microsurges of

LH and testosterone may occur, although the apparent incidence is low [Klotz, 2008]. The initial flare response may be managed with simultaneous antiandrogen administration, such as with bicalutamide.

Recently, GnRH antagonists, in particular degarelix, [Firmagon, 2016], have become available as an alternative form of medical castration. Degarelix, an injectable peptide, has been approved in some countries for the treatment of patients with advanced prostate cancer. As a GnRH antagonist, degarelix achieves medical castration and PSA response with no initial agonist activity within the first 1 to 2 weeks of administration, and effectively can obviate the need for concomitant antiandrogen treatment. Post-hoc analyses of degarelix trials [Tombal, 2010] suggest that it may have additional advantages regarding disease response or secondary relapse; however, such differences require confirmation in prospective studies. Because of the need for monthly depot injections, with large volumes and accompanying local reactions, the use of degarelix in clinical practice has remained low.

Relugolix, previously known as TAK-385, is a potent and highly selective oral small molecule antagonist for the human GnRH receptor. For patients, relugolix may offer the advantages conferred by a direct receptor antagonist, including a more rapid onset of action and the absence of clinical flare or worsening of symptoms from the initial rise in androgens caused by GnRH agonists, as well as having the added convenience and relative comfort of oral dosing.

2.2. Relugolix

2.2.1. Indication

Relugolix is being developed as a once daily oral medication for the treatment of advanced prostate cancer. The proposed dose of relugolix is 120 mg administered orally once daily following a loading dose of 360 mg (three 120-mg tablets) on Day 1.

2.2.2. Pharmacology

Relugolix is an orally-active, potent, highly-selective, high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes the human GnRH receptors present on the gonadotrophin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in testosterone in men and estradiol and progesterone levels in women. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels,

respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 μg·hr/mL, which is ~51 times higher than the estimated exposure (area under the concentration-time curve [AUC]) in men receiving 120 mg once daily (0.469 μg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 μg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥ 100 mg/kg (estimated C_{max} of 4.0 μg/mL), but did not prolong the QT interval in a human Thorough QT study at doses up to 360 mg (C_{max} of 0.181 μg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and 3 phase 2 studies have been completed. In addition, 6 clinical studies evaluating relugolix are ongoing, including 2 phase 1 studies, 2 phase 2 studies in men with prostate cancer (US and Europe), and 2 phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least one dose of relugolix, including 158 women receiving relugolix 40 mg once daily for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of testosterone in male subjects and estradiol in female subjects. After oral administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The PK and pharmacodynamics of relugolix have been evaluated and appear to be similar in Western and Asian volunteers, despite the lower mean body mass index observed in Asian volunteers.

A relative bioavailability and food effect study was conducted using the global phase 3 prostate cancer formulation of 120 mg relugolix. After administration with a high-fat, high-calorie breakfast, the C_{max} and AUC of relugolix were reduced, on average, by 21.4% and 18.8%, respectively.

In the phase 1 study C27001, serum LH, FSH, dihydrotestosterone, and testosterone concentrations were determined in healthy men following single and multiple oral doses of relugolix or placebo for up to 28 days. Loading doses of ≥ 160 mg on Day 1 were used to shorten the time to testosterone suppression. Relugolix caused an immediate and effective suppression of LH, FSH, and testosterone. After 14 days of once daily dosing, mean LH and serum testosterone concentration profiles were similar for the 40, 80, and 180 mg relugolix dose cohorts. LH, FSH, and testosterone concentrations began decreasing 2 to 6 hours postdose on Day 1 and remained suppressed through Day 14. However, the relugolix once daily maintenance dose was a major determinant of sustained testosterone suppression. Profound castration (defined as average testosterone levels < 20 ng/dL or 0.7 nmol/L) was achieved with 40, 80, or 180 mg once daily for 14 days; however, 20 mg once daily was insufficient in maintaining adequate suppression of serum LH and testosterone concentration levels during the second week.

In healthy, older men receiving 14 or 28 days of dosing, effective castration was consistently achieved over 14 and 28 days dosing at daily doses of 40 to 180 mg (14 days) and 80 to 160 mg (28 days). Use of a loading dose for up to 3 days (or once daily doses of ≥ 160 mg) resulted in castration levels of testosterone (< 50 ng/dL or 1.7 nmol/L) within 24 to 48 hours. Results obtained after 28 days of dosing suggested that the likely minimal, fully effective maintenance dose for sustained castration would be relugolix ≥ 80 mg once daily. Doses of 80 mg and 120 mg were moved forward into phase 2 development.

Relugolix is to be administered in the fasted state (at least 1 hour before or 2 hours after a meal), as food decreases the extent of relugolix absorption by approximately 20%. The exposure of relugolix is increased by inhibitors of P-glycoprotein up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 (CYP) 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong QTc at single doses of 60 or 360 mg.

2.2.4.2. Clinical Studies in Men with Prostate Cancer

One phase 1 study and 2 phase 2 studies have been conducted evaluating relugolix in men with prostate cancer.

Study TB-AK160108 is an ongoing multicenter phase 1, open-label, dose range-finding study conducted in hormone treatment-naïve Asian patients with non-metastatic prostate cancer. The study consists of a dose-rising phase (Part A) and an expansion phase (Part B). In Part A, a loading dose of relugolix (320 or 360 mg) was administered on Day 1 followed by once daily dosing on Days 2 through 28, with the dosage dependent on the individual cohort of 3 to 4 patients each. In Part B, 30 patients receive a maximum of 96 weeks treatment at doses of 80 and 120 mg once daily (N = 15 each arm, loading dose of 320 mg on Day 1). Testosterone reduction by both doses of relugolix was rapid and sustained through 48 weeks. Both the 80- and 120-mg once daily doses were evaluated in phase 2 clinical studies.

Study C27003 is a phase 2 study that enrolled men in North America or the United Kingdom requiring 6 months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily following a single oral loading dose of 320 mg (N = 65) or to degarelix 80 mg subcutaneously every 4 weeks following a single loading dose of 240 mg (N = 38) for 24 weeks. External beam radiation therapy was initiated for most patients between Week 13 and Week 15.

Relugolix 120 mg administered orally once daily rapidly suppressed testosterone levels below the castration threshold (50 ng/dL [1.7 nmol/L]) within the first week of therapy and maintained those levels from the end of Week 4 through at least 24 weeks. The levels of testosterone suppression achieved by relugolix were similar to those achieved by monthly injections of degarelix. Profound castration rates below the lower testosterone threshold of < 20 ng/dL (0.7 nmol/L) were also similar in the relugolix and degarelix groups (Table 2-1).

Table 2-1 Study C27003: Sustained Castration Rates (Percentage of Men Achieving Testosterone Suppression to < 50 ng/dL [1.7 nmol/L]) through 24 Weeks

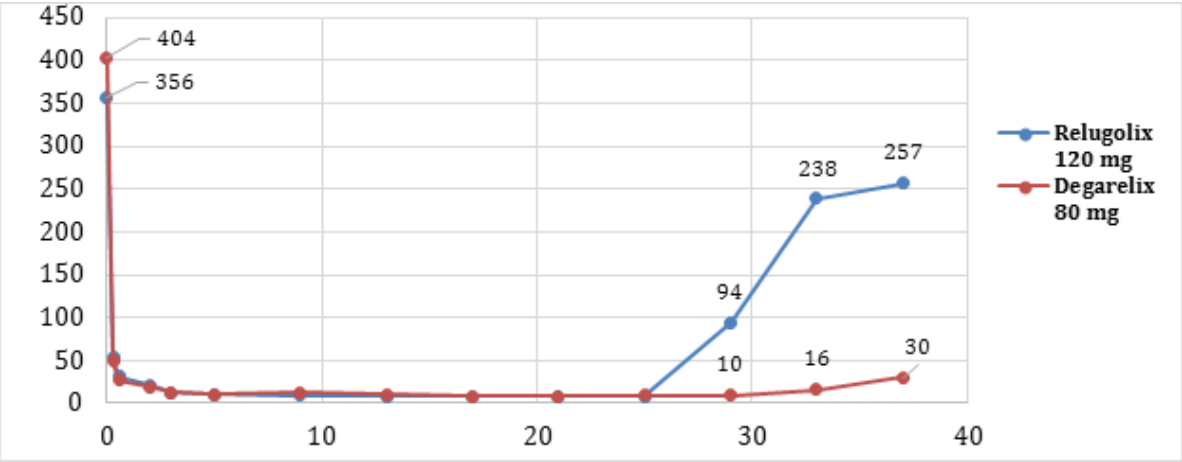
	Relugolix 120 mg QD[a] N = 65	**Degarelix 80 mg Q4W[b] N = 38**
Castration rate over 24 weeks, % (95% CI)	95% (87.1, 99.0)	89% (75.2, 97.1)

Note: Castration rate is defined as the estimated proportion of patients who have testosterone concentrations < 50 ng/dL at all scheduled visits Week 5, Day 1 to specific time point (Week 25, Day 1).
Abbreviations: CI, confidence interval; Q4W, once every 4 weeks; QD, once daily
a. Loading dose of 320 mg on Day 1
b. Loading dose of 240 mg on Day 1, then dosed every month

The percentage PSA reductions and absolute PSA values over time were consistent with the rapid testosterone reductions observed with both therapies and were similar between the relugolix and degarelix treatment arms. Prostate gland size was measured during screening and following 8 to12 weeks of study drug treatment. In both treatment groups, the average reduction in estimated prostate volumes was similar, approximately 30%. Following discontinuation of therapy at the end of 24 weeks, patients were followed for an additional 12 weeks to evaluate testosterone recovery and associated changes in PSA and quality of life. At the end of the follow-up period, approximately half of the patients receiving relugolix had recovered either to

the baseline testosterone value or to > 280 ng/dL, whichever was less, compared to only 6% of patients receiving degarelix (Figure 2-1).

Figure 2-1 Study C27003: Testosterone Recovery Following Discontinuation of Relugolix and Degarelix at Week 25



Note: Y-axis shows testosterone value (ng/dL); x-axis shows study week.

Study C27002 is a phase 2 study of relugolix and leuprolide acetate in patients with prostate cancer who require first-line androgen deprivation therapy, which is ongoing in North America. This study was designed to help plan the population, dosing, and assessment schedules for phase 3 studies in patients with advanced prostate cancer. Eligible patients in C27002 have evidence of advanced prostate cancer including either: 1) PSA biochemical relapse following primary surgical or radiation therapy of curative intent; 2) newly diagnosed metastatic prostate cancer; or 3) advanced localized disease for which immediate radiation or surgical therapy is not indicated. In this open-label, parallel group study, patients were randomized to receive 1 of 2 dose levels of oral relugolix (80 or 120 mg [patients randomized to relugolix received a loading dose of 320 mg on Day 1], N = 50 per group) or to an observation cohort to receive standard GnRH therapy with leuprolide acetate 22.5 mg administered by intramuscular injection every 12 weeks (N = 25). Relugolix or leuprolide acetate was administered for up to 48 weeks with patients randomized to leuprolide acetate receiving their last on-study 12-week depot injection at Week 37.

The primary objective of this phase 2 study was to evaluate the ability of relugolix to achieve and maintain testosterone suppression (< 50 ng/dL [1.7 nmol/L]) through Week 25. Results from the completed study C27002 demonstrate that both doses of relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold within the first week of therapy and maintained those levels in 91% of patients through 24 weeks of treatment (Table 2-2).

Table 2-2 Study C27002: Castration Rates (Percentage of Men Achieving Testosterone Suppression to < 50 ng/dL [1.7 nmol/L] through 24 Weeks)

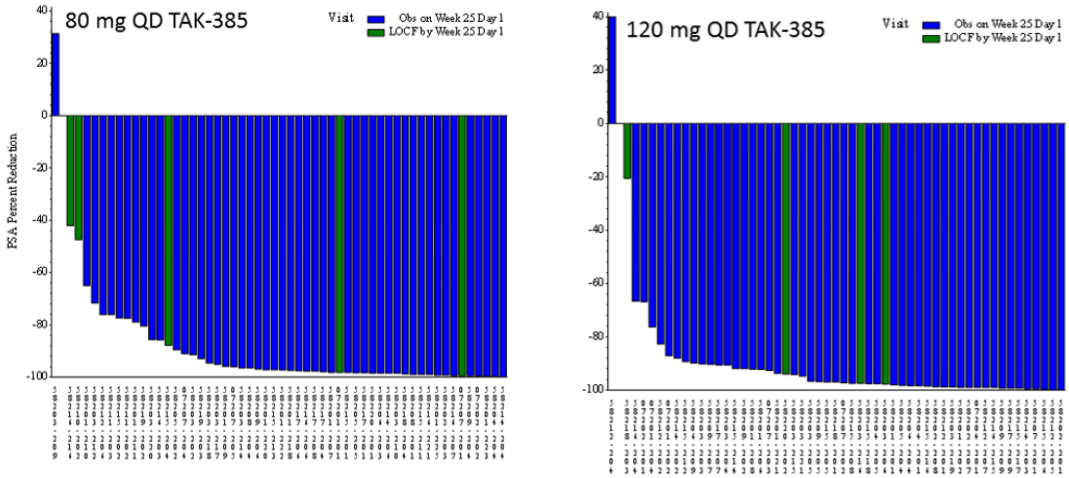
	Relugolix			Leuprolide Acetate 22.5 mg Q12W N = 24
	80 mg QD N = 56	120 mg QD N = 54	Total N = 110	
Patients with at least 1 dose of treatment, n	56	54	110	24
Castration rate[a] over 24 weeks				
n (%)	51 (91)	49 (91)	100 (91)	23 (96)
95% CI[b]	80.4-97.0	79.7-96.9	83.9-95.6	78.9-99.9
Profound castration rate[c] over 24 weeks				
n (%)	39 (70)	41 (76)	80 (73)	18 (75)
95% CI[b]	55.9-81.2	62.4-86.5	63.4-80.8	53.3-90.2

Abbreviations: CI, confidence interval; Q12W, once every 12 weeks; QD, daily

a. Castration rate was defined as the estimated proportion of patients who have testosterone concentrations < 50 ng/dL at all scheduled visits Week 5 Day 1 to specific time point.
b. The 2-sided 95% CI was calculated using the normal approximation method, if the number of non-castration patients was = 5 in any treatment arm, the exact CI was presented.
c. Profound castration rate was defined as the estimated proportion of patients who had testosterone concentrations < 20 ng/dL at all scheduled visits Week 13 Day 1 through specific time point.

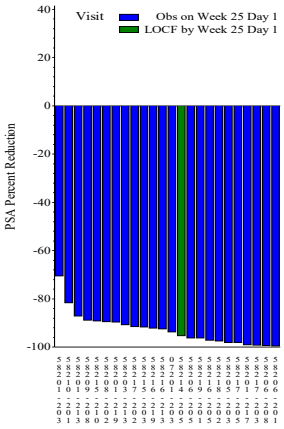
Castration to below the lower testosterone threshold of < 20 ng/dL was also similar in the 2 relugolix arms and to that observed in the leuprolide acetate arm. On average, in patients receiving relugolix, testosterone decreased to below the castration threshold of 50 ng/dL (1.7 nmol/L) by the Day 4 visit, and to below the profound castration threshold of 20 ng/dL (0.7 nmol/L) by the Week 5 visit. In contrast, in patients receiving leuprolide acetate, testosterone levels rose during the first 1 to 2 weeks of therapy and then declined to castrate levels by Week 5. PSA responses between the 2 relugolix arms and leuprolide acetate were similar as demonstrated by PSA waterfall plots showing the reduction in PSA from baseline for individual patients (Figure 2-2 [relugolix] and Figure 2-3 [leuprolide acetate]).

Figure 2-2 Study C27002: Waterfall Plots of Prostate-Specific Antigen Percent Reduction by Dose of Relugolix at Week 25 Day 1



Note: Last observation carried forward method was used to impute percent prostate-specific antigen reductions for patients without an observation at Week 25 Day 1.
Abbreviations: LOCF, last observation carried forward; Obs, observed; PSA, prostate-specific antigen; QD, once daily; TAK-385, relugolix

Figure 2-3 Study C27002: Waterfall Plot of Prostate-Specific Antigen Percent Reduction by Leuprolide Acetate at Week 25 Day 1



Notes:
The leuprolide acetate dose was 22.5 mg every 12 weeks.
Last observation carried forward method was used to impute percent prostate-specific antigen reductions for patients without an observation at Week 25 Day 1.
Abbreviations: LOCF, last observation carried forward; Obs, observed; PSA, prostate-specific antigen

A more detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix

Investigator Brochure, Version 9.0, dated 09 November 2016, along with a full discussion of the safety profile of relugolix.

2.2.4.3. Clinical Safety of Relugolix in Men with Prostate Cancer

A full description of the safety data for relugolix from clinical trials is available in the Investigator Brochure. Overall, approximately 632 healthy volunteers (330 women, 302 men), 535 female patients with uterine fibroids (N = 229) or endometriosis (N = 306), and 218 male patients with prostate cancer received at least 1 dose of relugolix. Data from the 175 patients with prostate cancer who received relugolix in randomized, open-label, parallel-group phase 2 studies, C27002 and C27003, provide the basis for the frequency of expected adverse events associated with relugolix in the prostate cancer indication. The adverse drug reactions in the prostate cancer indication observed in the phase 2 studies include hot flush (59%), fatigue (26%), arthralgia (10%), nausea (5%), and gynecomastia (3%). No clinical evidence of PLD has observed in any relugolix clinical study.

Leuprolide Acetate 3-Month Depot

Leuprolide acetate depot is indicated for the palliative treatment of advanced prostatic cancer.

Leuprolide acetate acts as an agonist at pituitary GnRH (gonadotropin-releasing hormone) receptors. Leuprolide acetate has greater receptor affinity, reduced susceptibility to enzymatic degradation, and is approximately 100-fold more potent than the natural GnRH molecule. GnRH agonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, causing an initial release of both LH and FSH, which causes a subsequent increase in testosterone production from testicular Leydig cells. Initially, leuprolide acetate stimulates LH production, which in turn causes a surge of testosterone and dihydrotestosterone for 5 to 12 days before the ultimate inhibition of LH. This androgen surge of male hormones can cause a flare reaction ("clinical flare"), which may lead to an increase in bone pain, bladder obstruction, or other symptoms due to prostate cancer [Tolis, 1982; Schally, 1980; Waxman, 1985; Conn, 1991; Limonata, 2001].

Chronic stimulation by the GnRH agonist ultimately desensitizes the GnRH receptors, downregulating the secretion of gonadotropins, LH, and FSH, leading to hypogonadism and thus a dramatic reduction in testosterone and dihydrotestosterone, on which continued growth of prostate cancer cells depends. The fall in serum LH leads to a decrease in serum testosterone to castrate levels within 3 to 4 weeks after the start of treatment. Continued treatment maintains serum testosterone at castrate levels.

The decrease in testosterone production is generally reversible over time upon cessation of GnRH agonist therapy. However, testosterone production does not always return to baseline levels and may be related to the duration of GnRH agonist therapy, patient age, and other factors.

The flare phenomenon can be effectively prevented with antiandrogen therapy, which blocks the effect of the increased serum testosterone [Loblaw, 2004]. First generation antiandrogens such as flutamide, bicalutamide, and nilutamide bind to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone. They are often used in an attempt to limit the clinical sequelae produced by the hormonal surge resulting from GnRH agonist treatment.

The most common adverse reactions (> 10%) reported for marketed formulations of leuprolide acetate depot in common use include the following examples:

- Leuprolide (leuprorelin) acetate 11.25 mg: weight fluctuation, hot flash, hyperhidrosis, muscle weakness, bone pain, decreased libido, erectile dysfunction, testicular atrophy, fatigue, injection site reaction [Prostap 3 DCS, 2016]
- Leuprolide acetate 22.5 mg: hot flashes, ecchymoses, erythema, fatigue, injection site burning, injection site paraesthesia [Eligard, 2016]

In post marketing experience, mood swings, depression, rare reports of suicidal ideation and attempt, rare reports of pituitary apoplexy have been reported. Leuprolide has been associated with mild liver enzyme elevations (generally transient and asymptomatic) during therapy in 3-5% of patients; values above 3 times the upper limit of normal are rare, being reported in less than 1% of recipients. A risk of developing or worsening diabetes has been reported in men receiving this class of drug.

The package insert (approved labeling) for the leuprolide acetate study drug provided for this study should be referenced for warnings, precautions, and safety information.

3. STUDY OBJECTIVES AND ENDPOINTS

This phase 3 trial has 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit as listed briefly below and described in detail in the statistical analysis plan. Patients enrolled into this phase 3 trial will be randomized 2:1 to either relugolix 120 mg once daily following an oral loading dose of 360 mg on Day 1, or to leuprolide acetate 22.5 mg (or 11.25 mg Japan, Taiwan, and China) 3-M depot injection. Patients randomized to leuprolide acetate will also receive an antiandrogen if indicated at the discretion of the investigator.

The first criterion for the primary efficacy endpoint will evaluate only patients randomized to relugolix. The second criterion for the primary efficacy endpoint will evaluate the non-inferiority of patients randomized to relugolix to those randomized to leuprolide acetate as described below.

Objectives	Endpoints
Primary	
• To evaluate the ability of relugolix to achieve and maintain serum testosterone suppressed to castrate levels of ≤ 50 ng/dL (1.7 nmol/L) in patients with androgen-sensitive advanced prostate cancer.	The primary endpoint is the sustained castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 Day 1 (Study Day 337). • Evaluation Criterion 1: to determine whether the sustained castration rate (defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL [1.7 nmol/L] while on study treatment from Week 5 Day 1 through Week 49 Day 7) for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be at least 90% to meet this criterion. • Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot injection as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.
Secondary	
• To evaluate the time course and change in serum testosterone during treatment with relugolix;	• Describe effects on serum testosterone: o Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing on Week 1 Day 4 and prior to dosing on Week 3 Day 1; o Profound castration rate defined as the cumulative probability of testosterone suppression to ≤ 20 ng/dL (0.7 nmol/L) while on treatment from Week 25 Day 1 through Week 49 Day 1);

Objectives	Endpoints
• To evaluate the time course and magnitude of PSA reduction during treatment with relugolix;	• Describe effects on PSA: o Proportion of patients with confirmed PSA response (by Prostate Cancer Clinical Trials Working Group 3 [Scher, 2016]) at the Week 3 and Week 5 visits; o Proportion of patients with PSA concentration < 0.2 ng/mL [0.2 µg/L] at the Week 25 visit;
• To evaluate testosterone recovery following discontinuation of relugolix;	• Time to testosterone recovery in approximately 100 patients randomized to relugolix and approximately 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of leuprolide acetate 3-M depot);
• To evaluate quality of life using validated patient-reported outcome instruments;	• Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable during the Follow-up and/or End of Treatment visits; • Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as the EuroQol EQ-5D-5L questionnaire, at regular intervals during treatment, and as applicable during the Follow-up visits;
• To evaluate the safety of relugolix 120 mg once daily in men with androgen-sensitive advanced prostate cancer;	• Incidence of adverse events; • Incidence of abnormalities in clinical laboratory data;

Objectives	Endpoints
• To evaluate the effect of relugolix and leuprolide acetate on endocrine pharmacodynamic parameters;	• Endocrine marker effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for: o LH at the Day 4, Week 5, Week 25, and Week 49 visits; o FSH at the Day 4, Week 5, Week 25, and Week 49 visits; o Dihydrotestosterone at the Week 5, Week 25, and Week 49 visits; o Sex hormone binding globulin at the Week 5, Week 25, and Week 49 visits;
• To collect relugolix plasma concentration data to further evaluate relugolix population PK and the relationship between relugolix exposure and serum testosterone; and	• Predose relugolix plasma concentrations;
• To characterize the relugolix plasma PK parameters in a subset of patients from China and Japan;	• Single and repeat-dose plasma relugolix PK parameters such as C_{max}, $AUC_{0-\tau}$, and t_{max}.
• To describe the time course and magnitude of PSA progression and development of castration-resistant prostate cancer during treatment with relugolix;	• Time to castration-resistance during the 48-week treatment • Time to PSA progression
Exploratory	
• To explore the overall survival of patients treated with relugolix; and	• Overall survival defined as time from randomization to date of death prior to data cutoff date;
• To explore the contribution of genetic variance on drug response.	• The presence of polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The HERO study is a phase 3 multinational randomized, open-label, parallel-group study to evaluate the safety and efficacy of relugolix in patients with androgen-sensitive advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy. Relugolix is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist that lowers testosterone by inhibiting pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Relugolix 120 mg orally once daily or leuprolide acetate depot suspension 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) every 3-months (3-M) will be administered

to patients with prostate cancer who require androgen deprivation therapy. This study will evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) for 48 weeks in patients with androgen-sensitive advanced prostate cancer.

To be eligible for the study, a patient must be, in the opinion of the investigator, a candidate for at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer and must not be a candidate for surgical therapy. Eligible patients include those with evidence of biochemical relapse (rising PSA) following local primary intervention with curative intent, newly diagnosed metastatic disease (excluding metastases to the brain), and/or advanced localized disease. Patients may receive radiotherapy, cryotherapy or high frequency ultrasound no sooner than 2 months after initiation of androgen deprivation therapy. Patients may be included if they have not previously received androgen deprivation therapy for more than 18 months, and if the androgen deprivation therapy was completed at least 3 months prior to baseline. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot. Patients previously treated with taxanes or expected to receive taxanes after initiation of androgen deprivation therapy are excluded, as are patients receiving androgen deprivation therapy adjuvant or neoadjuvant to radiotherapy as primary definitive therapy. Baseline serum testosterone must be ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L) to be enrolled.

Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg once daily following a loading dose of 360 mg on Day 1 or 3-M depot of leuprolide acetate 22.5 mg (or 11.25 mg in Japan, Taiwan, and China). After randomization, patients in the leuprolide acetate arm may receive an antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator. Randomization will be stratified by geographic region, presence of metastatic disease (metastases in regional lymph node[s] are considered N1 and will, therefore, be stratified as non-metastatic), and age.

A total of approximately 1100 patients from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region are planned to be enrolled in this study, including approximately 390 patients with metastatic advanced prostate cancer and approximately 138 Chinese patients (enrolled in China and Taiwan).

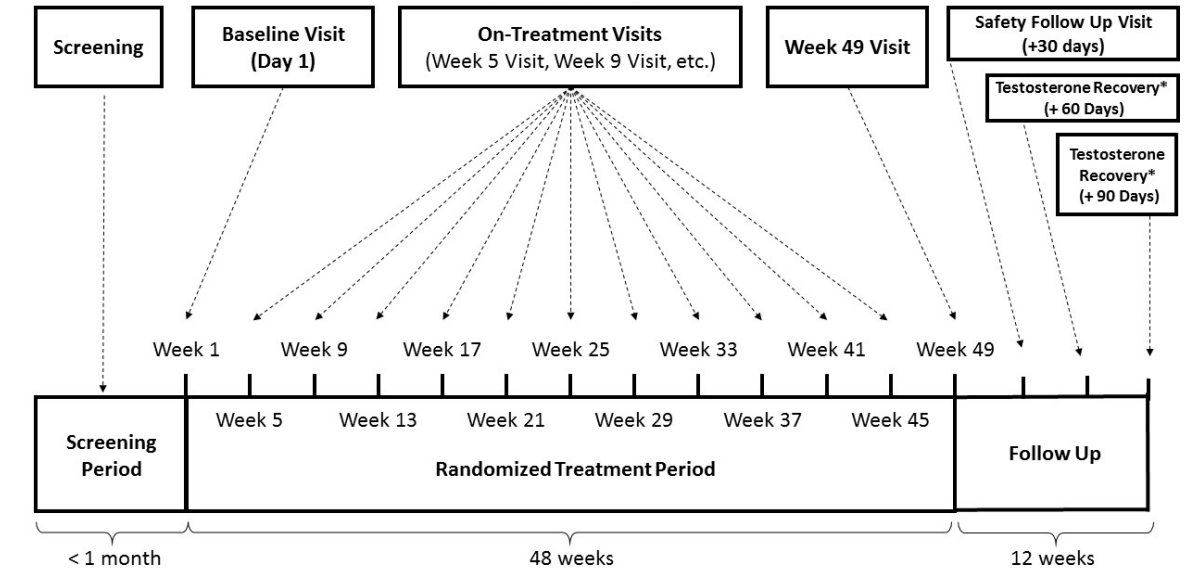
The study includes a Screening Period of up to 28 days, a Treatment Period of 48 weeks, and a Follow-up Period of up to 90 days. Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed. Eligible patients will receive study treatment for 48 weeks. During that time, testosterone and PSA will be assessed monthly and patient-reported outcomes (EORTC-QLQ-C30, EORTC-QLQ-PR25, EuroQol EQ-5D-5L) will be assessed approximately every 3 months during the Treatment Period and more frequently during the Follow-up Period. Additional serum endocrine evaluations will include: LH, FSH, dihydrotestosterone, and sex hormone binding globulin. Relugolix PK samples will be collected throughout the study. Full PK profiles will be determined in a subset of patients in China and Japan. Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead ECG, and visual acuity tests.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]), should be encouraged to remain on study and, if indicated, may receive radiotherapy as prescribed by the investigator. In the setting

of rising PSA patients may also receive enzalutamide after the confirmation of PSA progression. For patients requiring other systemic antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.

A schematic of the overall study design is provided in Figure 4-1.

Figure 4-1 Schematic of Study Design



Relugolix dosed daily (Baseline Day 1 – Week 48 Day 7)
Leuprolide Acetate dosed every 12 weeks (Baseline Day 1, Week 13 Day 1, Week 25 Day 1, and Week 37 Day 1)
*+60 Days and +90 Days Testosterone Recovery visits in subset of patients

4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is designed to establish the safety and efficacy of relugolix 120 mg orally once daily in men with advanced prostate cancer who require at least 1 year of continuous androgen deprivation therapy for androgen-sensitive disease. This study will focus on the primary objective of evaluating the ability of relugolix to achieve and maintain suppression of serum testosterone to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) in patients with advanced prostate cancer. During the Treatment Period of the study (Day 1 to Week 49 [Study Day 337]), patients will be randomized to one of the study treatment arms: oral loading dose of relugolix (360 mg) followed by 120 mg once daily of relugolix or leuprolide acetate 3-M depot injection of 22.5 mg (or 11.25 mg Japan, Taiwan, and China) at 12-week intervals for 48 weeks. Patients treated with leuprolide acetate will also receive an antiandrogen for 4 weeks or longer if indicated in the opinion of the investigator.

The study is designed to allow for global approvals, however, different regulatory agencies require different criteria for the demonstration of efficacy. The United States (US) Food and Drug Administration (FDA) requires, for approval, a primary efficacy criterion to determine whether the sustained castration rate (defined as the cumulative probability of testosterone

≤ 50 ng/dL [1.7 nmol/L] while on relugolix study treatment from Week 5 Day 1 through Week 49 Day 1) is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion. The study includes a leuprolide acetate arm to meet the regulatory requirement of other regions to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot injection as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion.

In amendment 3, an additional secondary endpoint of TCR is included in the final analysis. TCR is defined as the time from the date of first dose to the date of PSA progression while castrated (PSA progression is defined by the Prostate Cancer Clinical Trials Working Group 3 guidelines [Scher, 2016] as the first increase in PSA of 25% or greater and 2 ng/mL or greater above the nadir with confirmation by a second PSA measurement at least 3 weeks later; for patients without declining PSA from baseline, PSA increase of 25% or greater and 2 ng/mL from baseline beyond 12 weeks will be considered PSA progression) or deaths due any reasons. PSA progression is indicative of castration-resistance, the onset of which signals a higher risk of negative clinical outcomes in prostate cancer. It has been shown that patients with low FSH levels have significantly longer TCR [Hoare, 2015]. Furthermore, prior GnRH receptor antagonist treatment has demonstrated an increased sustained suppression of FSH, compared with a GnRH receptor agonist, and a 45% reduction in risk of castration-resistance events at 1 year (HR = 0.55) [Crawford, 2011]. In previous clinical trials, relugolix was associated with greater suppression of FSH than leuprolide. This endpoint is regarded as clinically meaningful by both patients and physicians and is an independent predictor of survival [Williams, 2004; Hussain, 2006; Hussain, 2009; Proust Lima, 2008]. To further explore the potential for relugolix to delay the TCR, this protocol is being amended so that additional patients with metastatic advanced prostate cancer will be enrolled (to enroll approximately 390 metastatic patients). The choice to enrich the study with metastatic patients is due to a higher incidence of castration-resistance (PSA progression) in patients with metastatic disease.

The dose of relugolix selected is based on data from phase 1 and 2 studies demonstrating that oral doses of 80 mg and 120 mg once daily following an oral loading dose of 320 mg were able to suppress testosterone to castrate levels (see Section 2.2.4.2 and the Investigator Brochure). A loading dose of 360 mg (three 120-mg tablets) was selected for phase 3 so that only one tablet size was required. Leuprolide acetate 3-M depot injection was selected as the comparator as this is the GnRH agonist used most commonly as standard of care in the population under evaluation. Degarelix, an injectable GnRH antagonist, was considered, but was not used as it has limited market uptake attributed at least in part to a significant number of injection site reactions.

4.3. Selection of Study Population

Approximately 1100 men with advanced prostate cancer requiring androgen deprivation therapy will be enrolled in this study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region. Enrollment is defined as the time at which a patient is randomized to a treatment group and receives at least one dose of study drug.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor prior to randomizing the patient.

4.3.1. Inclusion Criteria

A patient will be eligible for inclusion in this study only if all of the following inclusion criteria are met prior to randomization, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a male aged 18 years or older on the day of signing and dating the informed consent form;
3. Has histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate;
4. Is a candidate for, in the opinion of the investigator, at least 1 year of continuous androgen deprivation therapy for the management of androgen-sensitive advanced prostate cancer with one of the following clinical disease state presentations:
   a. Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, such as surgery, radiation therapy, cryotherapy, or high-frequency ultrasound and not a candidate for salvage treatment by surgery; or
   b. Newly diagnosed androgen-sensitive metastatic disease; or
   c. Advanced localized disease unlikely to be cured by local primary intervention with either surgery or radiation with curative intent;

   Note: radiotherapy, cryotherapy, or high frequency ultrasound are allowed after 2 months of androgen deprivation therapy. Prior palliative radiation to sites other than the prostate bed is permitted.

   Note: Once 915 patients are enrolled worldwide, only patients with metastatic advanced prostate cancer will be eligible for the study in all regions, except China, where both metastatic and non-metastatic patients will continue to be enrolled.
5. Has a serum testosterone at the Screening visit of ≥ 150 ng/dL (1.50 ng/mL or 5.2 nmol/L);
6. Has a serum PSA concentration at the Screening visit of > 2.0 ng/mL (2.0 µg/L), or, when applicable, post radical prostatectomy of > 0.2 ng/mL (0.2 µg/L) or post radiotherapy, cryotherapy, or high frequency ultrasound > 2.0 ng/mL (2.0 µg/L) above the post interventional nadir;

   Note: If patient has had a radical prostatectomy then PSA must be > 0.2 ng/mL (0.2 µg/L) irrespective of any other treatment the patient has had.
7. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at initial screening and at baseline (refer to Appendix 1);
8. Is a male patient who, even if surgically sterilized (ie, status post vasectomy):

a. Agrees to use a male condom if having sex with a woman of childbearing potential or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or

b. Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception;

9. Must agree not to donate sperm from first dose of study drug through 4 months after the last dose of study drug;
10. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

4.3.2. Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

1. In the investigator's opinion, is likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating androgen deprivation therapy;
2. Previously received GnRH analog or other form of androgen deprivation therapy (estrogen or antiandrogen) for > 18 months total duration. If androgen deprivation therapy was received for ≤ 18 months total duration, then that therapy must have been completed at least 3 months prior to baseline. If the dosing interval of the depot is longer than 3 months, then the prior androgen deprivation therapy must have been completed at least as long as the dosing interval of the depot;
3. Previous systemic cytotoxic treatment for prostate cancer (eg, taxane-based regimen);
4. Metastases to brain per prior clinical evaluation;
5. *Removed*;
6. Scheduled for major surgery after baseline;
7. History of surgical castration;
8. Active malignancy beyond prostate cancer ***with the exception*** of any of the following:
   - Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ carcinoma of any type
   - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for ≥ 2 years
   - Any other cancer from which the subject has been disease-free for ≥ 5 years

   The medical monitor should be contacted for any questions regarding this exclusion criterion.
9. Abnormal laboratory values at the Screening visit that suggest a clinically unstable underlying disease, or the following laboratory values:
   a. Serum gamma-glutamyl transferase > 2.0 x ULN;

b. Serum ALT and/or AST > ULN;

c. Total bilirubin > ULN (unless secondary to Gilbert's syndrome or the pattern is consistent with a diagnosis of Gilbert's syndrome) or;

d. Serum creatinine > 2.0 mg/dL (176.8 µmol/L);

e. Platelets < 100 x 10^3/µL or history of bleeding disorder;

f. Hemoglobin < 10.0 g/dL (100 g/L);

g. Leukocytes (WBC) < 3 x 10^3/µL (3 GI/L);

h. Absolute neutrophil count < 1.5 x 10^3/µL (1.5 GI/L);

10. Hemoglobin A1c (HbA1c) > 10% in patients previously diagnosed with diabetes mellitus. HbA1c > 8% in patients whose diabetes mellitus is previously undiagnosed (excluded patients may be rescreened after referral and evidence of improved control of their condition);
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (hepatitis A virus IgM positive), hepatitis B (HBsAg positive), or hepatitis C (HCV antibody positive, confirmed by HCV ribonucleic acid);
12. Known human immunodeficiency virus infection;
13. Any of the following within 6 months before Baseline Day 1:

    a. Myocardial infarction;

    b. Unstable angina;

    c. Unstable symptomatic ischemic heart disease;

    d. New York Heart Association (NYHA) class III or IV heart failure

    e. Thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events);

    f. Any other significant cardiac condition (eg, pericardial effusion, restrictive cardiomyopathy, severe untreated valvular stenosis, or severe congenital heart disease);

14. The following ECG abnormalities are excluded:

    a. ECG evidence of acute ischemia;

    b. Q-wave infarction, unless identified 6 or more months before the Screening visit;

    c. QTc > 470 msec, measured by Fridericia's formula [QTcF = QT/(RR^0.33)]. If the QTc is prolonged in a patient with a pacemaker, the patient may be enrolled in the study if confirmed by the medical monitor;

    d. Congenital long QT syndrome;

    e. Active conduction system abnormalities. Examples of active conduction system abnormalities include the following:

        - Mobitz II second degree heart block without a permanent pacemaker in place;
        - Third degree heart block without permanent pacemaker in place;

- Untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
- Clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes;
- Uncontrolled atrial fibrillation (patients with chronic stable atrial fibrillation on stable anticoagulant therapy or patients with stable cardiac rhythm controlled by a pacemaker are allowed);

The following exceptions are allowed: First degree atrioventricular (AV) block, second degree AV block Type 1 (Mobitz Type 1/Wenckebach type), or right bundle branch block.

15. Uncontrolled hypertension despite appropriate medical therapy (sitting blood pressure of greater than 160 mmHg systolic and/or 100 mmHg diastolic at 2 separate measurements no more than 45 minutes apart during the Screening visit). Patients may be re-screened after referral and further management of hypertension;
16. Hypotension, as indicated by systolic blood pressure < 84 mmHg on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming upright position;
17. Bradycardia as indicated by a heart rate of < 45 beats per minute on the ECG at the Screening or Baseline Day 1 visit;
18. Treatment with any investigational product within 28 days or 5 half-lives (whichever is longer);

    Exception: treatment for prostate cancer with any investigational products where the mechanism of action is testosterone lowering. In this circumstance, there must be a minimum 12-month treatment free interval.
19. *Removed*;
20. Previous treatment with relugolix in a clinical study;
21. Patient is a study site employee or is a primary family member (spouse, parent, child, or sibling) of a site employee involved in the conduct of the study;
22. Known gastrointestinal disease or procedure that could interfere with the oral absorption or tolerance of relugolix, including inability to swallow whole tablets or conditions that may interfere with absorption at the level of the small intestine. Examples of such conditions include but are not limited to Crohn's disease, gastric bypass, active peptic ulcer disease, and gastrectomy. The medical monitor should be contacted for any questions regarding this exclusion criterion;
23. Use or planned use of any medication listed in the prohibited medications table (see Section 5.10.1) without the appropriate washout period;
24. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;

25. Has a prior (within 1 year of the Screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
26. Any other medical or psychiatric condition that, in the opinion of the investigator, would interfere with completion of treatment according to this protocol.
27. Weight ≥ 400 pounds (181 kg) or has a body mass index ≥ 50;

4.4. Other Eligibility Criteria Considerations

Patient eligibility may require additional or repeat assessments such as safety labs, vital signs, or ECG during the Screening Period.

To assess any potential impact on patient eligibility with regard to safety, the investigator is referred to the Investigator Brochure for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) used in this study.

4.5. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the Screening Period. Study site personnel will access the interactive voice/web recognition system (IWRS) to assign a screening identification number to a potential patient.

For patients who provide informed consent and subsequently do not meet eligibility criteria, or withdraw consent are considered screen failures and are not randomized. Study site personnel should ensure that the source record includes documentation for the screen failure (eg, medical history, eligibility criteria, procedures performed).

Patient numbers assigned to patients who become screen failures are not to be reused. Patient identification numbers will be assigned to eligible patients at randomization, as described in Section 4.6.

4.6. Method of Assigning Patients to Treatment Group and Patient Identification Number

After a patient is screened and the investigator determines that the patient is eligible for enrollment, the site staff will complete the Randomization Authorization Form and send it to the sponsor (Myovant Sciences GmbH) or sponsor designee per the instructions in the investigator site file. The sponsor (or designee) will approve the patient's enrollment in writing. Once the site has received approval, the patient may undergo the Baseline Day 1 visit. The site will randomize the patient to treatment by using the IWRS during the patient's Baseline Day 1 visit. The IWRS will assign the patient identification (ID) number. This number will identify the patient for the duration of the study. A study treatment kit number will be available at the site according to the randomization code.

4.7. Removal of Patients from Therapy

Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Week 49 visit on the Schedule of Activities. The End of Treatment is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.

Follow-up visits to assess safety will be performed in all study patients. If the patient plans to start alternative androgen deprivation therapy less than 30 days after the End of Treatment visit, the Safety Follow-up visit may occur earlier, before the start of the alternative androgen deprivation therapy. Testosterone recovery will be evaluated in approximately 100 patients randomized to relugolix and approximately 50 patients to leuprolide acetate who complete 48 weeks of study drug treatment and, in the opinion of the investigator, are candidates for intermittent androgen deprivation therapy and will not be offered alternative androgen deprivation therapy upon completion of study therapy. These patients will return for the 60- and 90-day follow-up Testosterone Recovery visits.

The safety and/or compliance events shown in Table 4-1 will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved.

Table 4-1 Removal of Patients from Treatment

Reason	Comment
Adverse event or intercurrent illness	Any intolerable adverse event to the patient that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued
Failed to meet eligibility criteria post randomization	If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health
Dose hold	Relugolix dose hold that exceeds 10 consecutive days
Patient not meeting criteria for testosterone suppression to castrate level	Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]), should be encouraged to remain on study and, if indicated, may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide after the confirmation of PSA progression. For patients requiring other systemic antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.

Reason	Comment
Laboratory abnormality defined by protocol: ALT or AST > 8 x ULN; or ALT or AST > 5 x ULN and persists for more than 2 weeks; or ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or INR > 1.5; or ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)	If any of these liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status).
Confirmed QTcF prolongation of more than 500 msec, in the absence of a pacemaker, as read by a cardiologist	If QTc prolongation of > 500 msec in the absence of a pacemaker occurs, the ECG must be repeated. Confirmed QTc prolongation, measured by Fridericia's formula [QTcF = QT/(RR^0.33)], will result in removal of the patient from treatment.
Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist that may be related to study drug treatment	
Gross noncompliance with protocol	Patients who are, in the opinion of the investigator or the medical monitor, non-compliant with the protocol's requirements
Patient decision	Patients may permanently discontinue study treatment at any time for any reason. Following study drug discontinuation, patients should attend the protocol-required safety follow-up visit.
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime as described in Section 10.3.3. The sponsor will terminate this study following completion of study objectives, or earlier if deemed necessary.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; INR, international normalized ratio; QTc, QT interval corrected for heart rate; QTcF, QT interval corrected for heart rate using the Fridericia formula; ULN, upper limit of normal

Once study drug has been discontinued, all study procedures outlined for the Week 49 visit will be completed as specified in the Schedule of Activities (Section 1.1). The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who withdraw from treatment will not be replaced.

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. Patients randomized to relugolix should be counseled to notify the investigator in the event of intercurrent illness to determine if the study drug treatment can be continued. Every effort should be made to ensure the patient's compliance with study drug treatment, including calling patients to reschedule missed visits.

In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should attempt at least 3 documented telephone calls and, if necessary, a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.8. Contraception/Pregnancy Avoidance

It is not known what effects relugolix has on human pregnancy or development of the embryo or fetus. Therefore, male patients should avoid impregnating a female partner.

A patient must use a condom if having sex with a pregnant woman. Patients must not donate sperm from first dose of study drug through 4 months after the last dose of study drug.

Nonsterilized male patients should use a male condom, either alone or in addition to effective methods of contraception used by a female partner of childbearing potential, through defined periods during and after study treatment as specified below. Examples of effective contraceptive methods include condoms, hormonal contraceptives, and intrauterine devices.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to one of the following:

- Use a male condom if having sex with a woman of childbearing age or a pregnant woman, during the entire study Treatment Period and through 4 months after the last dose of study drug; or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods for the female partner, and withdrawal are not acceptable methods of contraception.

5. TREATMENTS

5.1. Treatments Administered

Patients enrolled in this study will be randomized 2:1 to receive oral relugolix 120 mg following a loading dose of 360 mg on Day 1, or leuprolide acetate 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) 3-M depot injection (plus antiandrogen for the first 4 weeks or longer if indicated in the opinion of the investigator). Randomization will be stratified by geographic region, presence

of metastatic disease (metastases in regional lymph node[s] are considered N1 and will, therefore, be stratified as non-metastatic), and age**.**

Approximately 1100 patients will be enrolled in the study from approximately 200 study centers in North and South America, Europe, and the Asia-Pacific region.

Study treatment is defined as either oral relugolix or leuprolide acetate injection (see Table 5-1).

Table 5-1 Description of MVT-601-3201 Study Drugs

	Study Treatment	
Product name:	Relugolix	Leuprolide Acetate 3-M Depot
Formulation description:	Round film coated pink tablet	
Dosage form:	Tablet	
Unit dose strength and dosage level:	120 mg, following a single-loading dose of 360 mg	22.5 mg (11.25 mg in Japan, Taiwan, and China)
Route of Administration / Duration	Oral / 48 weeks[a]	Subcutaneous or intramuscular / 48 weeks[a]

a. Duration of treatment is 48 weeks during the Treatment Period; the last leuprolide acetate injection occurs 12 weeks before the end of the Treatment Period.

5.2. Identity of Investigational Product

Relugolix has the chemical name N-(4-(1-(2,6-difluorobenzyl)-5-((dimethylamino)methyl)-3-(6-methoxy-3-pyridazinyl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-6-yl)phenyl)-N'-methoxyurea.

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using the US Pharmacopeia and the National Formulary excipients.

5.3. Randomization and Stratification

Patients are assigned to one of two treatment arms in accordance with the randomization schedule using an integrated randomization system (IWRS).

At Baseline Day 1, patients will be randomized in a 2:1 ratio to one of the following treatment arms:

Treatment Arm	Randomized Treatment	Approximate Number of Patients
Arm A	Relugolix 360 mg (three 120 mg tablets) single oral loading dose on Day 1 followed by 120 mg orally once daily	610
Arm B	Leuprolide acetate, 22.5 mg 3-M depot[a] injection (or 11.25 mg in Japan, Taiwan, and China)	305

a. Antiandrogen is administered for the first 4 weeks or longer if indicated, in the opinion of the investigator.

Randomization will be stratified by geographic region, presence of metastatic disease, and age as follows:

- Geographic Region
  - Europe;
  - North and South America; or
  - Asia and Rest of World.
- Presence of Metastatic Disease
  - Metastatic disease diagnosed on locally-read imaging by abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) or bone scan at the time of the Baseline Day 1 visit; or
  - No evidence of metastatic disease by locally-read imaging (metastases in regional lymph node(s) are considered N1 and will, therefore, be stratified as non-metastatic).
- Baseline Age
  - ≤ 75 years old; or
  - > 75 years old.

After the first 915 patients are enrolled, enrollment in China will continue for metastatic and non-metastatic patients until the target number of Chinese patients is reached (138 patients). In the rest of the world, only metastatic patients will continue to be enrolled until approximately 390 metastatic patients for the overall study are accrued.

5.4. Directions for Administration

Relugolix

Relugolix 120-mg tablet strength will be available as immediate-release film-coated tablets. These tablets will be presented in 45-tablet bottle packaging and dispensed to patients every 4 weeks at scheduled study visits.

All protocol-specific criteria for administration of study drug must be met and documented prior to study drug administration. Study drug will be dispensed by study personnel only to eligible patients who are under the supervision of the investigator or identified subinvestigator(s). If a blood draw or any study procedure coincides with a meal, the study procedure will take precedence, followed by the blood draw, and then the meal.

At the Baseline Day 1 visit, the site will administer a single loading dose of oral relugolix 360 mg (3 tablets).

Patients randomized to relugolix will be instructed to take one tablet on an empty stomach at least 1 hour before breakfast once daily. If the dose is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

Patients may consume water ad libitum. Patients should swallow the study medication whole and not chew it or manipulate it in any way before swallowing.

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK and pharmacodynamic samples are collected.

Leuprolide Acetate

Leuprolide acetate 3-M depot injection, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China), will be administered every 12 weeks. Leuprolide acetate 3-M depot will be administered on Day 1 at the clinic, then at 12-week intervals (see Schedule of Activities, Section 1.1) and investigators should follow product instructions provided by the manufacturer. An antiandrogen may be administered for the first 4 weeks or longer if indicated, as determined by the investigator, and/or as indicated by disease status (eg, in patients with extensive localized symptomatic disease or with metastatic disease).

Possible antiandrogen options include, but are not limited to, bicalutamide, flutamide, and nilutamide.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that is related to study drug and cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted if the investigator believes it is in the best interest of the patient to interrupt relugolix dosing until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 10 consecutive days for evaluation and treatment of an adverse event. Patients may subsequently be re-started on study drug, with the written approval of the sponsor (or designee).

5.6. Dose Escalation, Dose Reduction, and Dose Interruption

Neither dose escalations nor dose reductions are allowed in the study.

Every effort should be made to continue relugolix administration through treatment-emergent adverse events unless they are grade 3 or 4 and related to study drug, or the investigator believes it is in the best interest of the patient to interrupt relugolix dosing. Of note, patients on leuprolide acetate 3-M depot injection continue to receive GnRH agonist therapy because it is impossible to discontinue treatment.

If the grade 3 or 4 adverse event improves to grade 0, 1, or 2 after holding the dose, or if the adverse event is no longer believed to be related to study drug, the patient may be rechallenged at the same dose at the discretion of the investigator and medical monitor. If the adverse event remains grade 3 or grade 4 after treatment discontinuation and the investigator continues to believe the adverse event is related to study drug, study drug treatment should be discontinued permanently.

5.7. Storage, Packaging, and Labeling

Relugolix will be packaged in bottles containing forty-five 120-mg tablets of relugolix. Additional details regarding the packaging of relugolix are provided in the Investigator Brochure and investigator site file.

Leuprolide acetate 11.25 mg or 22.5 mg 3-M depot injection will be packaged and labeled for clinical trial use.

Relugolix medication should be stored in an appropriate, limited-access, secure location, protected from light, in the original bottles and within a temperature range at 15°C to 25°C (59°F to 77°F) with excursions permitted up to 30°C (86°F).

A daily temperature log of the drug storage area must be maintained every working day.

Study drug must be stored under the conditions specified and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Patients will be instructed to store study drug at room temperature out of the reach of children.

Further guidance and information for final disposition of unused study drug are provided in the investigator site file. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Refer to the leuprolide acetate product labeling for information regarding the proper storage and handling of leuprolide acetate.

5.8. Blinding

Blinding is not applicable; this is a randomized open-label study.

5.9. Study Drug Accountability and Treatment Compliance

Patients should bring all unused study drug to each study visit. Study drug accountability will be conducted and results will be recorded as the primary source of study drug accountability. If a patient is persistently noncompliant with the study treatment, it may be appropriate to withdraw the patient from the study.

All patients should be reinstructed regarding dosing compliance during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance.

Patients randomized to relugolix should be counseled to notify the investigator in the event of intercurrent illness to determine if the study drug treatment can be continued. Should a patient need a surgery of any kind, please contact the medical monitor. Every effort should be made to ensure the patient's compliance with study drug treatment, including calling patients to reschedule missed visits.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-2 provides examples of systemic medications that are prohibited prior to the first dose of study medication until the End of Treatment visit and the Follow-up Period is complete. This list is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class. Patients may "wash out" of these prohibited medications prior to dosing based on the periods provided in Table 5-2.

Any investigational agent for the treatment of prostate cancer where the mechanism of action is testosterone lowering, including agents that are commercially available for indications other than prostate cancer that are under investigation for the treatment of prostate cancer, are also prohibited for at least 12 months prior to the first dose of study medication.

Table 5-2 Prohibited Medications and Washout Periods

Drug Class	Examples		Minimum Washout Period[c]
GnRH analogues	Leuprolide acetate injection[a] Goserelin acetate injection		At least one dosing interval of the depot preparation; minimum of 3 months[d]
GnRH antagonists	Degarelix		At least one dosing interval of the depot preparation; minimum of 3 months[d]
Antiandrogens[a]	Bicalutamide Flutamide	Nilutamide Enzalutamide[b]	3 months
CYP17 inhibitors	Abiraterone acetate + prednisone		3 months
Other androgen suppressing agents or androgens	Estrogens Ketoconazole Testosterones	Megestrol acetate Progestogens	3 months
5-alpha reductase inhibitors	Finasteride Dutasteride		4 weeks 6 months

Drug Class	Examples		Minimum Washout Period[c]
Class IA an III antiarrhythmics	Amiodarone Procainamide	Quinidine Sotalol	2 weeks (3 months for amiodarone)
Moderate and strong CYP3A and Pglycoprotein- inducers	Bosentan Carbamazepine Efavirenz Etravirine Mitotane Modafinil Nafcillin	Phenobarbital Phenytoin Rifampin St John's Wort Primidone Rifabutin Rifapentine	1 week Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.
Moderate/strong P-glycoprotein inhibitors	Amiodarone Azithromycin Captopril Carvedilol Clarithromycin Conivaptan Cyclosporin Diltiazem Dronedarone Eliglustat Erythromycin	Felodipine Itraconazole Ketoconazole Lapatinib Lopinavir/Ritonavir Quercetin Quinidine Ranolazine Ticagrelor Verapamil	1 week (3 months for amiodarone) (3 months for ketoconazole) Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.
High-dose biotin supplements[e]	Vitamin B7 CoEnzyme R	Vitamin H	
Herbal therapies[f]	Ginkgo biloba Kava kava	Ginseng	2 weeks or 5 half-lives (whichever is shorter)

Abbreviation: CYP, cytochrome P450

a. Unless randomized to leuprolide acetate control arm of this study. After randomization, antiandrogen therapy is permitted for the first 4 weeks or longer of leuprolide acetate treatment.
b. Enzalutamide is allowed for the treatment of castration-resistant disease that occurs on study (rising prostate-specific antigen in the setting of testosterone suppressed to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) after the confirmation of PSA progression.
c. Minimum washout period is calculated from the date of last dose of prohibited medication to the first day of study drug.
d. Patients with cumulative previous androgen deprivation therapy > 18 months are excluded, regardless of washout period.
e. See Section 5.10.1.1 for additional details. For questions about which biotin supplements may be permitted, please consult with the study Medical Monitor.
f. For patients taking herbal remedies, questions regarding appropriate wash-out period should be addressed on a case-by-case basis with the study Medical Monitor.

5.10.1.1. High-Dose Biotin Supplements

In November 2017, the FDA issued a safety communication on biotin interference intended for healthcare professionals [FDA, 2017]. Briefly, the communication made the following recommendations:

- Talk to your patients about any biotin supplements they may be taking, including supplements marketed for hair, skin, and nail growth.
- Be aware that many laboratory tests, including but not limited to cardiovascular diagnostic tests and hormone tests, that use biotin technology are potentially affected, and incorrect test results may be generated if there is biotin in the patient's specimen.
- Communicate to the laboratory conducting the testing if your patient is taking biotin.
- If a laboratory test result doesn't match the clinical presentation of your patient, consider biotin interference as a possible source of error.
- Know that biotin is found in multivitamins, including prenatal multivitamins, biotin supplements, and dietary supplements for hair, skin, and nail growth in levels that may interfere with laboratory tests.
- Report to the laboratory test manufacturer and the FDA if you become aware of a patient experiencing an adverse event following potentially incorrect laboratory test results due to biotin interference.

A threshold 'high level' biotin dose has not yet been defined by FDA.

Study Investigators should discuss with study patients about any biotin supplements they may be taking. For patients taking biotin supplements, the investigator should assess if it is possible to discontinue use of these supplements. In cases where the investigator believes a patient is taking high doses of biotin and discontinuation of this supplementation is not in the best interest of the patient, the investigator should contact the Medical Monitor to assess the potential impact on study laboratory test results.

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded. At a minimum, the drug generic name, dose amount, route of administration, start date, and stop date will be recorded in the source documents and the eCRF.

If alternative androgen deprivation therapy is initiated prior to 30 days after the last relugolix dose, record the alternative androgen deprivation therapy as a concomitant medication.

Patients with disease progression during the treatment period, in the setting of testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]), should be encouraged to remain on study and, if indicated, may receive radiotherapy as prescribed by the investigator. In the setting of rising PSA patients may also receive enzalutamide after the confirmation of PSA progression. For patients requiring other systemic antineoplastic therapy during the treatment period, the investigator should contact the medical monitor.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.6. Further details of the procedures are provided in the investigator site file.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Section 1.1). The study is divided into 3 periods: Screening Period, Treatment Period, and Follow-up Period. Unscheduled visits may also occur as needed to evaluate patients.

6.2. Screening Period (Day -28 to Day -1)

The Screening Period will be from Day -28 through Day -1. At the Screening visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent before any study-specific procedures are conducted, unless the procedures are part of routine standard of care. The informed consent process must be documented in the patient's clinical record.

The investigator will assess and confirm the eligibility of each patient and determine that each patient will maintain study drug compliance during the treatment period. All screening procedures results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

The following assessments will be performed:

- Complete medical history, including detailed prostate cancer history;
- Vital signs, weight, and height;
- 12-lead ECG;
- ECOG performance assessment;
- Complete physical exam and visual acuity assessment;
- An abdominopelvic CT or MRI and a bone scan should be performed and read locally to determine the presence of metastatic disease within 60 days prior to randomization. However, if CT or MRI demonstrates presence of metastatic disease, a bone scan is not required. If metastatic disease is not present on CT or MRI, then a bone scan is also required.
- Demographics;
- Laboratory data collection (see Section 1.1);
- Verify inclusion/exclusion criteria; and
- Concomitant medications and adverse events.

A Randomization Authorization Form must be submitted to the sponsor for approval prior to conducting the Baseline Day 1 visit.

6.3. Treatment Period (Day 1 to Week 49 [Study Day 337])

Baseline Day 1 Visit

Study site personnel should ensure that an approved Randomization Authorization Form is in the patient's file before proceeding with the randomization and Day 1 visit procedures. Patients will be randomized to either relugolix or leuprolide acetate 3-M depot injection 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) (see Section 5.3).

The following assessments will be performed:

- Patient-reported outcome questionnaires (EQ-5D-5L, EORTC-QLQ-PR25, and EORTC-QLQ-C30)
    - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Medical history;
- Vital signs and weight;
- 12-lead ECG;
- ECOG performance assessment;
- Symptom-based physical examination;
- Verify inclusion/exclusion criteria;
- Concomitant medications and adverse events;
- Randomize the patient;
- Laboratory collection (see Section 1.1); and
- Study drug management:
    - If study drug administration is not logistically feasible on the same day as randomization, Day 1 will be defined as the day of the first dose.
    - If the patient is randomized to relugolix, site personnel will administer a single loading dose of oral relugolix 360 mg (3 tablets) and then dispense study drug to the patient and instruct on daily dosing of 120 mg (1 tablet) and the importance of medication compliance (see Section 5.4);
    - If the patient is randomized to leuprolide acetate, site personnel will administer the injection in the clinic.

Day 4 and Weeks 2 and 3 Visits (Visit Window ± 2 days)

The following assessments will be performed:

- Vitals signs;
- Laboratory collection (see Section 1.1); and
- Concomitant medications and adverse events.

Note: The Week 2 visit will only occur for patients who are part of the Japan or China subset for PK analysis.

Weeks 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, and 45 Visits (Visit Window ± 7 Days)

Importantly, patients randomized to relugolix should be called 7 days before each visit to ensure the patient is compliant with study drug medication.

The following assessments will be performed:

- Patient-reported questionnaires will be completed on the electronic tablet provided (Weeks 5, 13, 25, and 37 only)
    - Patients will complete the questionnaires before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs, weight
    - Weight will be collected only on Weeks 13 and 25;
- 12-lead ECG (Weeks 5, 13, and 25 only);
- ECOG performance assessment (Week 25 only);
- Symptom-based physical examination (except Week 25);
- Complete physical exam and visual acuity assessment (Week 25 only);
- Laboratory collection (see Section 1.1)
    - Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose, approximately 24 hours after the previous dose. Patients may be dosed in the clinic at these visits, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing.
- Concomitant medications and adverse events; and
- Study drug management:
    - For patients randomized to relugolix,
        - Perform study drug accountability;
        - Dispense study drug. Patients may be dosed in the clinic, provided the dose can be administered at least 2 hours after food; food should be withheld for 1 hour after dosing;
        - Remind patients on importance of medication compliance.
    - For patients randomized to leuprolide acetate,
        - Site will administer leuprolide acetate in clinic every 12 weeks (Weeks 13, 25, and 37).

Week 49 or (Early Termination of Study Drug) (Visit Window ± 7 Days)

- For patients receiving relugolix, a member of the site team will call the patient 7 days before the Week 49 visit to remind the patient of the need for compliance with their study medication;
- Patient-reported outcome questionnaires
    - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs, weight;
- 12-lead ECG;
- ECOG performance assessment;
- Complete physical exam and visual acuity assessment;

- Laboratory collection (see Section 1.1);
    - Blood samples for PK analysis will be collected for all patients assigned to the relugolix treatment arm. Samples will be collected predose, approximately 24 hours after the previous dose.
- Concomitant medications and adverse events; and
- Study drug management:
    - For patients randomized to relugolix,
        - Perform study drug accountability.

6.4. Follow-up Period

The study day in which the Follow-up visit occurs is relative to when the patient takes his last dose of study drug. The End of Treatment is defined as the last dose of relugolix or 12 weeks after the last leuprolide acetate injection.

30-Day Safety Follow-up Visit (Visit Window ± 7 Days)

A Safety Follow-up visit should occur 30 days after the End of Treatment and may occur earlier for patients who are starting alternative androgen deprivation therapy or do not complete 12 weeks of study treatment. Adverse events should continue to be collected and recorded through 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Serious adverse events and concomitant medications will be collected from the signing of the informed consent form until the Safety Follow-up visit approximately 30 days after the last dose of study drug.

All other study procedures should be completed before the start of alternative androgen deprivation therapy.

The following assessments will be performed:

- Patient-reported questionnaires
    - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs and weight;
- 12-lead ECG;
- ECOG performance assessment;
- Symptom-based physical examination;
- Laboratory collection (see Section 1.1); and
- Concomitant medications and adverse events.

Testosterone Recovery Visit (Visit Window ± 7 Days)

Patients who have started alternative androgen deprivation therapy will not participate in the 60- and 90-day follow-up visits. Approximately 100 patients randomized to receive relugolix and approximately 50 patients randomized to receive leuprolide acetate who complete the 48 weeks of study drug treatment and, in the opinion of the investigator, are candidates for intermittent androgen deprivation therapy will be included in the Testosterone Recovery 60- and 90-day Follow-up visits. These patients will discontinue relugolix after 48 weeks of treatment and will be offered a period off androgen deprivation therapy.

The following assessments will be performed:

- Patient-reported outcome questionnaires
  - Patients will complete the questionnaires on the tablet provided before other study procedures, such as blood draws and physical examinations, are performed;
- Vital signs;
- Symptom-based physical examination;
- Laboratory collection (see Section 1.1); and
- Concomitant medications.

Health Status Survey

During the final weeks prior to database lock, sites will be asked to contact all study participants or their immediate family regarding the current health status of previously enrolled/completed study patients. If the site is unsuccessful in contacting the patient and/or immediate family, the site may access hospital records or publicly available sources such as national registries, newspaper obituaries, and social networking websites.

6.5. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The following activities should be completed at an Unscheduled visit: recording of the date and reason for the visit in the patient's source documents, concomitant medication review and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment and collection of a PK sample if indicated, 12-lead ECG, study drug compliance and dispensation, etc. may be conducted as needed. See Schedule of Events (see Section 1.1) for tests that may be performed if indicated at an unscheduled visit. Consult with the medical monitor, if needed, to discuss Unscheduled visit testing.

6.6. Study Procedures

6.6.1. Efficacy-Related Procedures

6.6.1.1. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, testosterone, dihydrotestosterone, sex hormone binding globulin, and PSA will be collected predose at the visits indicated in the Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. Testosterone samples may be analyzed at a second laboratory to confirm non-castrate levels (Section 1.1).

Serum LH, FSH, dihydrotestosterone, sex hormone binding globulin, and PSA samples will be analyzed at a central laboratory.

PSA will also be used to evaluate biochemical progression per Prostate Cancer Clinical Trials Working Group 3 guidelines [Scher, 2016].

Analysis of serum samples for testosterone is detailed below:

Testosterone Assessment

Serum concentrations of testosterone will be obtained as indicated in the Schedule of Activities (see Section 1.1).

Testosterone will be assayed using a liquid chromatography-tandem mass spectrometry method sensitive at least as low as 5 ng/dL (0.17 nmol/L) for all measurements.

Between Week 5 and Week 49 visits (inclusive), testosterone samples that are above castrate level (> 50 ng/dL) will be reported to the investigator at the respective study site. Testosterone samples may be subject to reanalysis by liquid chromatography/mass spectrometry and/or immunoassay sensitive to at least as low as 10 ng/dL.

Instructions for collection and processing of blood specimens are provided in the investigator site file.

6.6.1.2. Pharmacokinetic Sample Collection

Relugolix

Pharmacokinetic samples will only be collected in patients randomized to relugolix study drug.

Blood samples for pharmacokinetic analysis of relugolix will be collected at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients may take their dose of study drug in the clinic at these visits. Study drug will be administered on an empty stomach or at least 2 hours before food, and food will be withheld for 1 hour after dosing. The date and time of their previous dose of study drug (ie, the dose the day before the clinic visit) will be accurately recorded.

Ideally, predose samples should be collected approximately 24 hours (±6 hours) after the previous dose of relugolix, although samples collected outside of this window would not be considered a protocol deviation.

If the study patient inadvertently took the study drug at home on the morning of the clinic visit, the date and time of that dose should also be accurately recorded and the PK sample collected, which may be used for population PK modeling.

Plasma from the Week 5 and Week 13 visits in all patients will be analyzed for relugolix plasma concentration. Analysis of other individual patient plasma samples will be performed on a case-by-case basis (such as those patients with non-castrate testosterone levels).

Collection, processing, storage, and shipping instructions will be provided in the investigator site file. Plasma analysis of relugolix will be performed by the sponsor (or designee).

Leuprolide Acetate

For patients on leuprolide acetate, in the event of non-castrate testosterone levels, a blood sample may be taken for potential analysis of leuprolide acetate plasma concentration, following discussion with the medical monitor

China and Japan Pharmacokinetic Subset

In a subset of patients from China and approximately 20 patients from Japan that are randomized to relugolix, additional relugolix PK samples will be collected on Day 1, Day 4, and Week 2 visits (see Schedule of Activities in the protocol synopsis, Section 1.1). The actual date and time of study drug administration and the date and time of each PK sample will be accurately recorded.

All samples from the China and Japan subset will be analyzed for plasma relugolix concentrations. Collection, processing, storage, and shipping instructions will be provided in the investigator site file. Plasma analysis of relugolix will be performed by the sponsor (or designee).

6.6.1.3. Pharmacogenomics Sample Collection

Whole Blood Sample for Germline Deoxyribonucleic Acid

Pharmacogenomic analysis may be conducted to examine the contribution of genetic variance on drug response, for example, its efficacy and safety. Participation of study patients in pharmacogenomic sample collection is optional. A pharmacogenomics sample will be collected from patients at all participating study centers, with individual patient consent and per local ethics and regulatory standards. The sample will be retained for germline deoxyribonucleic acid (DNA) analysis of potential genetic determinants of drug safety, drug efficacy or disease response, and drug metabolism.

Every patient must sign informed consent/be consented in order to participate in the sampling of whole blood for DNA analysis. This research may be used to develop a better understanding of the safety and efficacy of relugolix and other study drugs, to increase understanding of the disease/condition being studied, and for improving the efficiency, design and study methods of future research studies.

Two venous whole blood sample (4 mL per sample) for the analysis of germline DNA will be collected at Day 1 from all patients who have provided informed consent. The DNA samples are expected to be collected at the Day 1 visit, but if necessary, may be collected at any visit after randomization. If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible. Germline DNA analysis may be conducted to investigate the contribution of genetic variance on drug response, for example, its efficacy and safety. As pharmacogenomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples.

Individual blood samples for germline DNA analysis, including the result of any analyses and corresponding information will be identified only by a code in a computer database.

The whole blood samples for DNA analysis will be stored securely at the sponsor's location or its designated central laboratory vendor until 10 years after completion of this study (HERO, MVT-601-3201) and/or until the drug development of relugolix is no longer actively pursued by Myovant or its collaborators. The storage period for these samples may be adjusted by country in accordance with local regulatory and/or legal requirements for the storage of research samples.

Such changes will be reflected in the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) country-specific informed consent form. After that time, the samples will be properly destroyed by the central laboratory or designee following approval by the sponsor. The investigator will keep records linking the patient identity with the samples for the time required by applicable law. Patients who consent and provide a pharmacogenomic sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time.

Directions for sample collection and handling can be found in the investigator site file.

6.6.1.4. Quality of Life

European Quality of Life 5-Dimension 5-Level Assessment

The EuroQol EQ-5D-5L comprises 5 scales and an overall assessment of health status on a visual analogue scale (Appendix 2). The 5 scales include: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The original version, the EQ-5D-3L, includes 3 response options for each scale. However, a new 5 level-response-option version, the EQ-5D-5L, has been developed with the following response options: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. It is believed that the EQ-5D-5L is superior to the EQ-5D-3L in terms of feasibility, ceiling effects, discriminatory power, and convergent validity. The EQ-5D-5L index values will be calculated from the EQ-5D-5L descriptive system scores based on the Crosswalk value sets [Eligard, 2016; EuroQol Group, 1990; Brooks, 1996; Herdman, 2011; Janssen, 2013].

European Organisation for Research and Treatment of Cancer Assessments

The EORTC-QLQ-C30 [Fayers, 2001; Fayers, 2002] (Appendix 3) and the 25-item prostate cancer module EORTC-QLQ-PR25 [Spry, 2006] (Appendix 4) will be administered as specified in the Schedule of Activities (see Section 1.1).

The EORTC QLQ-C30 core measurement will be used to capture distal outcomes, including physical, social functioning, and overall health-related quality of life. The QLQ-C30 core questionnaire incorporates 30 questions comprising 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality of life scale. Several single-item symptom measures are also included. It is a reliable and valid measure of health-related quality of life in patients with cancer and takes about 11 minutes to administer. The instrument has been validated and used in many countries [Aaronson, 1993].

The EORTC-QLQ-PR25 is the 25-item Prostate Cancer module (P25) of the EORTC. The EORTC-QLQ-PR25 contains 3 additional symptom scales (urinary, bowel, sexual) and 5 treatment-related items.

6.6.2. Safety-Related Procedures

6.6.2.1. Weight, Height, and Body Mass Index

Height and weight will be measured during screening (within 28 days before the first dose of study drug). Weight will be obtained at additional time points as specified in the Schedule of

Activities (see Section 1.1). Patients should have weight and height measured while wearing indoor clothing and with shoes removed.

6.6.2.2. Vital Signs

Vital sign measurements include temperature, pulse rate, and seated measurement of diastolic and systolic blood pressure. For each patient, temperature should be recorded using the same modality throughout the entire study. Patients should be sitting at rest for 5 minutes before blood pressure is measured. When vital sign measurements are scheduled at the same time as an ECG and blood draw, the vital signs, when possible, will be obtained immediately prior to the ECG and blood draw, and the blood draw will be collected at the scheduled time.

6.6.2.3. Physical Exams and Visual Acuity

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart, and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the baseline assessment.

Visual acuity will be evaluated at Screening, Week 25, and Week 49 by a standard visual eye chart. Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, he should wear his usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions (see the investigator site file for additional details).

Patients whose presenting visual acuity score is 90 or lower at the screening visit should be encouraged to obtain a diagnostic evaluation from an eye care provider (ie, an ophthalmologist or an optometrist). Any findings (ie, diagnoses) from the eye examination should be recorded as medical history.

Patients whose presenting visual acuity score at Week 25, Week 49, or Early Termination has decreased by 10 or more points from the screening visit must be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.

6.6.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the investigator site file and the protocol Schedule of Activities (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the patient ID number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Metabolic Panel**
Hematocrit Hemoglobin Leukocytes with differential Neutrophils and absolute neutrophil count Platelet (count)	Albumin Alkaline phosphatase ALT AST Bilirubin (total) Blood urea nitrogen Calcium Carbon dioxide Creatinine Chloride Serum gamma-glutamyl transferase Glucose Lactate dehydrogenase Magnesium Phosphate Potassium Sodium Urate	Total cholesterol High density lipoprotein cholesterol Low density lipoprotein cholesterol Triglycerides Hemoglobin A1c
Endocrine Panel	**Diagnostic Screening (investigator's discretion)**	
Serum testosterone Serum LH Serum FSH Serum sex hormone binding globulin	Hepatitis panel, according to CDC criteria	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FSH, follicle-stimulating hormone; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; LH, luteinizing hormone

A separate sample will be collected at the Day 1 visit and will be banked and tested for presence of hepatitis A, B, and C (hepatitis A antibody, IgM, hepatitis B core antibody, IgM, hepatitis B surface antigen, and hepatitis C antibody) if requested by the medical monitor for evaluation of abnormal liver function tests.

The central laboratory will perform laboratory tests for chemistry, hematology, and plasma and serum hormone levels.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

6.6.2.5. 12-Lead Electrocardiograms

A 12-lead ECG will be administered at the time points specified in the Schedule of Activities (Section 1.1). When an ECG is scheduled at the same time as vital signs and a blood draw, the ECG, when possible, will be obtained after the vital signs and prior to the blood draw; the blood draw will be collected at the scheduled time. ECGs will be read locally by a qualified physician.

If patients have a prolonged QTcF (> 500 msec), as measured by Fridericia's formula [QTcF = QT/(RR^0.33)], in the absence of a pacemaker, the ECG should be repeated and confirmed. Patients with a confirmed QTcF > 500 msec, in the absence of a pacemaker, as read by a cardiologist should be withdrawn. All abnormal ECG findings must be documented by the investigator as clinically significant or not.

6.6.2.6. Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient 30 days prior to the first dose of study drug until 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection will recorded in the eCRF (Exception: amiodarone will be reported if taken within 3 months prior to the first day of study drug). See Section 5.10.1 for a list of medications and therapies that are prohibited and/or allowed during the study.

6.6.2.7. Radiologic Assessment

CT imaging or MRI of the abdominopelvic region with contrast (except where contrast is medically contraindicated) and a bone scan must be obtained prior to randomization for each patient to determine the presence or absence of metastatic disease (metastases in regional lymph node[s] are considered N1 and will, therefore, be stratified as non-metastatic). The scans should be read locally and do not need to be repeated if a scan exists within 60 days prior to the Baseline Day 1 visit. However, if CT or MRI demonstrates presence of metastatic disease, a bone scan is not required. If metastatic disease is not present on CT or MRI, then a bone scan is also required.

Radiologic assessment is not included as part of the Schedule of Activities after randomization.

6.7. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study.

Exploratory testing for markers of cardiovascular disease, including tests such as plasma N-terminal pro- brain natriuretic peptide (NT-proBNP) or markers for ischemia, may be conducted using stored samples from patients who provided consent for this testing, to explore whether there are differences in measures of cardiovascular function between patients treated with relugolix and patients treated with leuprolide, to inform future studies.

Samples of 8 mL of whole blood for pharmacogenomics testing (see Section 6.6.1.3) will be collected. The need to conduct pharmacogenomic analysis may be identified after this study

(or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of his sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations including visual acuity assessment, vital signs, weight, ECGs, and clinical laboratory tests.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention; or
    - Requires interruption or discontinuation of study drug.

Events that **do not** meet the definition of an adverse event include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- The disease/disorder being studied, or expected progression;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen; and
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent).

Adverse events that occur during the study should be evaluated by the investigator and graded according to CTCAE (Appendix 5). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous". Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of study drug are permitted; however, study drug can be held for a period of up to 10 days for evaluation and treatment of an adverse event. The study drug may be restarted if deemed safe for the patient by the investigator.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events that jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local IRB/IEC.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's answers to the EQ-5D-5L will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in a partner will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered until the Safety Follow-up visit approximately 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first.

Serious adverse events will be collected from the signing of the informed consent form until the Safety Follow-up visit approximately 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide acetate injection, or the date of initiation of another

investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

Any event occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who continues to meet eligibility criteria and proceeds to dosing with study drug; the exception to this includes procedure-related pretreatment-emergent events which should be recorded as adverse events in the electronic data capture (EDC) system for those patients who remain eligible for study participation.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The definitions in Table 7-1 are to be used for the relationship of the adverse event to study drug.

Table 7-1 Causal Relationship to Study Drug

Relationship	Criteria
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (re-challenge) or withdrawal (de-challenge).
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE (see Appendix 5). For terms not specified with the CTCAE, the criteria in Table 7-2 should be used to determine the grade severity.

Table 7-2 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized Treatment Period or the Follow-up visit should be reported to the sponsor using the serious adverse event form within 24 hours of the study site personnel's knowledge of the event (see Section 7.6), even if the event does not meet serious adverse event criteria. Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 6.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or international normalized ratio (INR) >1.5
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1) AST or ALT increases to ≥ 3 x ULN; AND
2) Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3) Alkaline phosphatase value does not reach 2 x ULN; AND
4) No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease;
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus);
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
   - Alcoholic hepatitis;
   - Nonalcoholic steatohepatitis; or
   - Autoimmune hepatitis.

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

Using a serious adverse event report form, all serious adverse events must be reported **within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose or pregnancy of partner is available on the serious adverse event report form and is as follows:

Send completed Safety Report Forms to IQVIA (previously named QuintilesIMS; contact information as below and on the SAE Form):

Site Location	E-mail (Primary reporting method)	Fax Number (Secondary reporting method)
All Regions	PPD	PPD

For questions on Serious Adverse Event (SAE)/Adverse Event of Clinical Interest or events of overdose reporting, please call:

- North/South America: PPD
- Regional toll-free phone and fax lines distributed separately. Please refer to the investigator site file.

The initial report should include:

- Study number (MVT-601-3201);
- Site address and number;
- Investigator name;
- Patient ID number, sex, and age;
- Details of study drug administration;
- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity); and
- Causal relationship to the study drug.

If the patient died, the report should include the cause of death and whether or not the cause of death was related to study drug, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 240 mg within a 24-hour window is an overdose, except for the 360-mg loading dose. The sponsor does not recommend specific treatment for an overdose; supportive treatment should be provided as clinically applicable.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;

- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis); and
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If the partner of any patient becomes pregnant during the study or through 4 months after the last dose of study drug, the investigator must inform the sponsor of the pregnancy.

The patient should remain on study drug treatment, unless otherwise indicated.

If the patient agrees, the patient's pregnant partner should be notified and requested to sign a Release of Information form, permitting transfer of information regarding the pregnancy and outcome to the sponsor.

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the partner pregnancy report forms. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Benefit/Risk Assessment

Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

The risk assessment and mitigation strategies for this protocol are outlined in Table 7-3.

Table 7-3 Relugolix Potential Risks and Mitigation

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Stopping Criteria**
Hepatic Enzyme Increases Isolated increases in hepatic enzymes have been observed in prior clinical studies. Hepatic enzyme increases, considered an important potential risk of treatment with relugolix, are closely monitored in accordance with FDA guidelines for assessing drug-induced liver injury [FDA, 2009] in all relugolix studies.	Exclusion criteria for AST and ALT > ULN; total bilirubin values > ULN unless consistent with Gilbert's syndrome.	Liver chemistry will be monitored during the study. Appropriate liver stopping criteria and follow-up procedures are detailed in Section 7.5.2.
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual acuity will be evaluated during the study.
Risks Associated with Medical Castration Acute and subsequent chronic symptoms of medical castration (reduction of testosterone to ≤ 50 ng/dL [1.7 nmol/L]) include vasomotor symptoms or hot flushes, disturbed sleep related to vasomotor symptoms, decreased libido, and fatigue or loss of energy. These side effects are usually not severe and can be managed with anticipatory guidance. Long-term suppression of testosterone is associated with well-characterized risks including bone loss, decreased muscle mass, possible changes in insulin sensitivity with increased risk of diabetes, altered lipid metabolism, and possible increased risk of cardiovascular disease [Oefelein, 2002; Lopez, 2005; Diamond,1998; Keating, 2006; Braga-Basaria, 2006; Saigal, 2007; Tsai, 2007; D'Amico, 2007; Efstathiou, 2009].	-	Effects can usually be managed with appropriate anticipatory guidance (eg, diet and exercise programs) or supportive therapy when required (eg, lipid-lowering or bone-sparing agents).
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	-	Fasting lipids and glucose will be monitored during the study.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Stopping Criteria**
Loss of Bone Mineral Density Loss of bone mineral density is considered a potential risk of treatment with relugolix in the prostate cancer indication.	-	Fractures will be assessed through adverse event monitoring. Use of anti-resorptive bone therapy, such as bisphosphonates or denosumab, may be considered by the treating physician.

Abbreviations: ALT; alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; FDA, Food and Drug Administration; PLD, phospholipidoses; ULN, upper limit of normal

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the investigator site file with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and Good Clinical Practices. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

8.3. Independent Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will review available safety data, as appropriate, on a periodic basis throughout the conduct of the study. Details of the Data and Safety Monitoring Board will be captured in a charter prior to the start of the study.

8.4. Steering Committee

A Steering Committee consisting of experts in the field of prostate cancer and staff members of Myovant Sciences GmbH will be established to provide oversight for the clinical trial, study design, study conduct, data analysis, and presentation and publication of the study data. Details of the Steering Committee responsibilities will be captured in a separate charter.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan will describe the detailed statistical methods and analyses for this study. The statistical analysis plan will be prepared and finalized before database lock for the primary analysis.

There will be two analyses for the study, a primary analysis and a final analysis. The primary analysis of efficacy and safety will occur after approximately the first 915 patients have been randomized to the study and have had the opportunity to be evaluated for 48 weeks and complete the 30-day safety follow-up visit or discontinued early.

The secondary analysis will occur after approximately 390 metastatic patients have been to the study and have had the opportunity to be evaluated for 48 weeks of study treatment and complete the 30-day safety follow-up visit.

TCR in the subgroup of metastatic patients and the extended ITT population will be analyzed only at the time of the final analysis.

All confidence intervals will be 2-sided at an alpha level of 0.05 unless otherwise specified. The methodology to be used to maintain a study-wide type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 2:1, relugolix to leuprolide acetate 3-M depot. Randomization will be stratified by the following factors:

- Geographic Region: North and South America versus Europe versus Asia and Rest of World;
- Presence of Metastatic Disease (metastases in regional lymph node[s] are considered N1 and will, therefore, be stratified as non-metastatic): yes versus no;
- Baseline Age: ≤ 75 years old versus > 75 years old.

Stratified efficacy analyses will incorporate these 3 stratification factors unless otherwise specified.

After the first 915 patients are enrolled, enrollment in China will continue for metastatic and non-metastatic patients until the target number of Chinese patients is reached (138 patients). In the rest of the world, only metastatic patients will continue to be enrolled until approximately 390 metastatic patients are accrued.

9.2. Analysis Populations

The Intent-To-Treat (ITT) population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. This will be the primary population used for the efficacy analysis. Patients will be analyzed according to their randomized treatment assignment.

The Per-Protocol population will consist of those members of the ITT population who have no major protocol deviations as defined in the statistical analysis plan, considering the following protocol deviations but not limited to:

- Those who entered the study even though they did not satisfy the entry criteria;
- Those who developed withdrawal criteria during the study but were not withdrawn;
- Those who received the wrong treatment or incorrect dose;
- Those who received an excluded concomitant treatment.

The Per-Protocol population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT population. The Per-Protocol population will be used as a sensitivity analysis of the ITT population for the primary efficacy endpoint and secondary endpoints. The Per-Protocol population will be identified prior to the database lock.

The primary population for safety analyses will be the Safety population, defined as all patients who receive at least one dose of any study treatment. Patients will be analyzed according to the treatment actually received, regardless of their randomized treatment assignment.

9.3. Efficacy Analyses

9.3.1. Primary Endpoint Analyses

The primary endpoint will be analyzed in the initial 915 patients enrolled to the study. The primary efficacy endpoint is the sustained castration rate, defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (Study Day 29) through Week 49 (Study Day 337). This probability will be estimated for each treatment group using the Kaplan-Meier method with the confidence interval calculated using the exponential Greenwood formula via log-log transformation of the survival function. Patients who discontinue treatment prior to observing a testosterone level > 50 ng/dL (1.7 nmol/L) will be censored at the last testosterone assessment prior to discontinuation. Detailed censoring rules will be described in the statistical analysis plan.

There are 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit:

- Evaluation Criterion 1: to determine whether the sustained castration rate for relugolix is greater than or equal to 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group will be calculated and must be greater than or equal to 90% to meet this criterion.
- Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide acetate 3-M depot as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the 2 treatment groups will be calculated and must be greater than or equal to the non-inferiority margin of -10% to meet this criterion. The confidence interval of the treatment difference will be calculated using the formula $\hat{V}\left[\widehat{S_1}(t) - \widehat{S_2}(t)\right] = \hat{V}\left[\widehat{S_1}(t)\right] + \hat{V}\left[\widehat{S_2}(t)\right]$, where each of the variance of the Kaplan-Meier estimate will be calculated using the Greenwood's formula $\hat{V}\left[\hat{S}(t)\right] = \hat{S}(t)^2\left[\sum_{j:t_{(j)}\le t}\frac{d_j}{n_j(n_j-d_j)}\right]$; n_j denote the number of patients at risk at time $t_{(j)}$ and d_j denote the number of events observed at time $t_{(j)}$) [Lachin, 2000].

The evaluation criteria used for the primary efficacy endpoint assessment will be determined by regional regulatory requirements and will be prespecified in separate regional statistical analysis plans. The 2-sided type I error rates for the final analyses will be controlled at 0.05 separately for each regional analysis.

9.3.2. Secondary Endpoint Analyses

If the result of the primary endpoint is statistically significant, the secondary endpoints will be analyzed. The methods and procedures necessary to maintain a study-wide 2-sided type I error rate of 0.05 across primary and secondary endpoint testing will be described in the statistical analysis plan.

- Castration rate defined as the cumulative probability of testosterone suppression to ≤ 50 ng/dL (1.7 nmol/L) prior to dosing at Week 1 Day 4, and prior to dosing at Week 3 Day 1 will be summarized by treatment group using the Kaplan-Meier method;
- Profound castration rate defined as the cumulative probability of testosterone suppression of ≤ 20 ng/dL (0.7 nmol/L) while on treatment from Week 25 Day 1 through Week 49 Day 1 will be estimated for each treatment group using the Kaplan-Meier method. The difference in the cumulative probabilities between the relugolix group and the leuprolide acetate group will be provided, along with the 95% confidence interval calculated in the same manner as in the primary analysis of the primary endpoint;
- PSA response and percent change from baseline in PSA at Week 3 and Week 5 will be summarized and compared between the relugolix group and the leuprolide acetate group;
- Proportions of patients who have a PSA concentration < 0.2 ng/mL (0.2 µg/L) at Week 25 will be summarized by treatment group. The proportions will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in proportions;
- Time to testosterone recovery in approximately 100 patients randomized to relugolix and approximately 50 patients randomized to leuprolide acetate who complete 48 weeks of treatment and who do not start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last received leuprolide acetate 3-M depot injection) will be compared between the relugolix group and the leuprolide acetate group;
- Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains will be summarized by treatment group. The least square means at Week 49 will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in the least square means using a mixed model for repeated measures;
- Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as EQ-5D-5L will be summarized by treatment group. The least square means at Week 49 will be compared between the relugolix group and the leuprolide acetate group by constructing a 95% confidence interval for the difference in the least square means using a mixed model for repeated measures;
- Time to PSA progression;
    - PSA progression is defined per Prostate Cancer Clinical Trials Working Group 3 guidelines [Scher, 2016] as the first increase in PSA of 25% or greater and 2 ng/mL or greater above the nadir with confirmation by a second PSA measurement at least 3 weeks later. For patients without declining PSA from baseline, PSA increase of 25% or greater and 2 ng/mL from baseline beyond 12 weeks will be considered PSA progression

- TCR in the subgroup of metastatic patients and the extended ITT population will only be evaluated at the time of final analysis, when approximately 390 metastatic patients have been randomized to the study and have had the opportunity to be evaluated for 48 weeks of study treatment and complete the 30-day safety follow-up visit or discontinued early. TCR will be evaluated first in the subgroup of metastatic patients at a two-sided significance level of 0.05. TCR in the extended ITT population will be tested only if the two-sided p-value in the subset of metastatic patients is < 0.05.
    - TCR is defined as the time from the date of first dose to the date of PSA progression while castrated or death due to any reason, whichever occurs earlier. TCR will be analyzed using the Kaplan-Meier method. Treatment comparison with hazard ratios will be performed using Cox proportional hazards model.

Additional details of the secondary analyses will be described in the statistical analysis plan.

9.4. Safety Analyses

The safety analyses will be based on the Safety population. Safety will be assessed by summarizing and analyzing adverse events, laboratory analytes, vital signs, ECG parameters, and concomitant medications.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ class using MedDRA 19.1 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used for analyses. The National Cancer Institute CTCAE will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the baseline versus post-baseline results.

9.5. Pharmacokinetic Analyses

Plasma relugolix concentrations will be listed and summarized and included in the clinical study report.

PK data may be pooled with data from other studies in healthy male patients and patients with prostate cancer for population PK analysis, including evaluation of covariates of relugolix PK parameters, and for input into a population PK/pharmacodynamics models describing the relationship between relugolix exposure and serum testosterone [Ahsman, 2016]. These population PK analyses will be detailed further in a separate statistical analysis plan and report.

For patients from China and Japan in the PK subset, plasma relugolix PK parameters C_{max}, $AUC_{0-\tau}$, and t_{max} from Day 1 and Day 14 of dosing will be determined. Population PK or

PK/pharmacodynamic analyses may be conducted to explore the factors that affect relugolix exposure or to contribute to the assessment of the relationships between exposure and testosterone.

9.6. Endocrine Marker Analyses

Endocrine markers will be analyzed to see effects of relugolix and leuprolide acetate as measured as absolute value and change from baseline for:

- LH at Day 4, Week 5, Week 25, and Week 49 visits and/or follow-up visit(s);
- FSH at Day 4, Week 5, Week 25, and Week 49 visits and/or follow-up visit(s);
- Dihydrotestosterone at Week 5, Week 25, and Week 49 visits and/or follow-up visit(s);
- Sex hormone binding globulin at Week 5, Week 25, and Week 49 visits and/or follow-up visit(s).

9.7. Exploratory Analyses

Overall survival: Overall survival defined as time from randomization to date of death prior to data cutoff date. Kaplan-Meier methods will be used to describe survival distributions for each treatment arm.

Pharmacogenomic analyses may be conducted to examine the contribution of genetic variance on drug response, for example, its efficacy and safety, pending availability of samples. Polymorphisms in germline genes related to the hypothalamic-pituitary-androgen pathway, prostate cancer risk, or to drug metabolizing enzymes and transporter proteins that might be implicated in the drug disposition, safety, or efficacy of relugolix. These analyses will be detailed in a separate statistical analysis plan and associated reports.

9.8. Interim Analyses

There will be no planned interim efficacy analysis for the study.

9.9. Sample Size

To calculate the sample size required for the primary efficacy endpoint of this study, the following assumptions have been made:

- True probabilities of sustained testosterone suppression are 94% and 96% for relugolix and leuprolide acetate, respectively;
- 2:1 randomization ratio (relugolix:leuprolide acetate); and
- Dropout rate of 15%.

The assumed probability of sustained testosterone suppression for relugolix arm is 94%. It was estimated based on the predicted dose-response relationship for the effect of relugolix on testosterone suppression in patients with prostate cancer (data from phase 2 studies C27002 and C27003). The assumed castration rate of 96% for leuprolide acetate was based on the results from degarelix phase 3 registration program [Shore, 2013].

For Evaluation Criterion 1, 610 patients in the relugolix group will provide approximately 90% power to rule out a fixed probability of sustained testosterone suppression of < 90% at a two-sided type I error rate of 0.05.

For Evaluation Criterion 2, with the non-inferiority margin of -10% and an overall 2-sided type I error rate of 0.05, a total of approximately 915 patients (610 relugolix, 305 leuprolide acetate) will yield at least 99% power in declaring the non-inferiority of relugolix compared to leuprolide acetate.

The primary analysis will be performed separately for individual evaluation criterion using data collected through 48 weeks after enrollment of approximately 915 patients.

Approximately 915 patients will be randomized in order to fulfill the regulatory requirements of all participating countries included in the primary efficacy endpoint of this study.

The study is also powered for the secondary endpoint of TCR in the high-risk subgroup of metastatic patients. Approximately 107 confirmed castration-resistance events (PSA progressions while castrated or deaths due to any cause) will need to be observed (or approximately 390 metastatic patients will need to be enrolled) to detect a hazard ratio of 0.55 (relugolix versus leuprolide acetate) with 85% power with a two-sided type I error of 5%, assuming a castration-resistant event-free rate of 60% at 48 weeks for the control arm, an 18-month enrollment period, 12 months of additional follow-up, and a 15% dropout rate.

With a total of approximately 1100 patients (metastatic or non-metastatic) randomized into the study including approximately 138 Chinese patients, it is anticipated to observe approximately 149 confirmed castration-resistant events (PSA progression while castrated or deaths due to any cause). Assuming an 18-month enrollment period, 12 months of additional follow-up, and a 10% dropout rate the study will provide approximately 85% power to detect a hazard ratio of 0.6 (relugolix versus leuprolide acetate) with a two-sided type I error of 5%.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Council on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a US investigational new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) Part 312, subpart D, "Responsibilities of sponsors and investigators," 21 CFR Part 50, and 21 CFR Part 56, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR Part 54, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a

marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

A properly executed, written informed consent, in compliance with the Declaration of Helsinki, ICH Good Clinical Practice, US CFR for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27), and local regulations, will be obtained from each patient before entering the patient in the trial. The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

The investigator will provide copies of the signed informed consent form to each patient (or to the patient's legal representatives) and will maintain the signed original document within the patient's record file per local requirements. The investigator will also fully document the informed consent process in the patient's source records.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log

showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator Brochure, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories:

1) Investigator's study file: The investigator's study file will contain the Investigator Brochure, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents: The required source data should include the following for each patient:
   - Patient identification (name, date of birth, gender);
   - Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
   - Participation in the study (including study number);
   - Study discussed and date of informed consent;
   - Dates of all visits;
   - Documentation that protocol-specific procedures were performed;
   - Results of efficacy parameters, as required by the protocol;
   - Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
   - Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
   - Concomitant medication (including start and end date); and
   - Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the Investigator Brochure, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and

study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.5. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on the 1572 form and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization Screening Period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.6. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability including dates and lot numbers of all study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, patient ID number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

All records must be made available to the sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

Current ICH Good Clinical Practice guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (eg, pharmacist), and the following:

- That such deliveries are recorded, for example, on the sponsor-approved drug accountability log, or other sponsor-approved pharmacy log;
- That study drug is handled and stored safely and properly in accordance with the study protocol;
- That study drug is only dispensed to study patients in accordance with the protocol;
- That any unused study drug is returned to the sponsor-designated facility or standard procedures for the alternative disposition of unused study drug are followed and only after approval by the sponsor representative.

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drug to any persons except the patients in this study;
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs;
- The investigator/pharmacist will maintain a study drug inventory. The inventory will include details of material received and a clear record of when they were dispensed and to which patient;
- The investigator/pharmacist agrees to conduct a final drug supply inventory on the drug accountability record at the conclusion or termination of the study. It must be possible to reconcile delivery records with those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries must be signed by the person responsible;
- Used or unused study drug may be destroyed at the study site according to standard institutional procedures if the sponsor agrees with the procedure, and after drug accountability has been conducted by the sponsor or representative. Unused study drug not destroyed at the site must be returned to the sponsor-designated facility at the end of the study or upon expiration.

10.1.7. Inspections

During the course of the study and after study completion, it is likely that one or more quality assurance audits will be undertaken by authorized sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the protocol as well as recognized Good Clinical Practice guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed time. By signing this protocol, the investigator grants permission to the sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.8. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers (eg, http://www.clinicaltrials.gov) before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH Good Clinical Practice guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may terminate the study and send a written notice of the termination along with the reasons to the investigator. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants' interests.

If the investigator intends to terminate participation in the study, the investigator must immediately inform the sponsor and provide the reason to it.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993 Mar 3;85(5):365-76.

Ahsman M, Faessel HM, Snelder NS, MacLean D, Vis P. Modelling and simulation of oral GnRH Antagonist TAK-385 and testosterone-lowering response in Prostate Cancer Patients to Optimize Trial Design and Dose Selection. Population Analysis Group Europe. 2016; Abstr 5847. Available at: http://www.page-meeting.org/print_abstract.asp?abstract_id=5847. Accessed: 11 January 2017.

Bosland MC. Testosterone treatment is a potent tumor promoter for the rat prostate. *Endocrinology*. 2014 Dec;155(12):4629-33.

Braga-Basaria M, Dobs AS, Muller DC, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol*. 2006 Aug 20;24(24):3979-83.

Brooks R. EuroQol: the current state of play. *Health Policy*. 1996 Jul;37(1):53-72.

Cersosimo RJ, Carr D. Prostate cancer: current and evolving strategies. *Am J Health Syst Pharm*. 1996 Feb 15;53(4):381-96; quiz 446-8.

Conn PM, Crowley WF Jr. Gonadotropin-releasing hormone and its analogues. *N Engl J Med*. 1991 Jan 10;324(2):93-103.

Crawford ED, Tombal B, Miller K, et al. A phase III extension trial with a 1-arm crossover from leuprolide to degarelix: a comparison of gonadotropin-releasing hormone agonist and antagonist effect on prostate cancer. *J Urol*. 2011; 186(3):889-897.

D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol*. 2007 Jun 10;25(17):2420-5.

Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. *Cancer*. 1998 Oct 15;83(8):1561-6.

Efstathiou JA, Bae K, Shipley WU, et al. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. *J Clin Oncol*. 2009 Jan 1;27(1):92-9.

Eligard. Prescribing Information. Tolmar Pharmaceuticals, Inc., Fort Collins, CO, USA. Revised 02/2016.

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990 Dec;16(3):199-208.

Fayers P, Aaronson NK, Bjordal K, et al. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: EORTC; 2001.

Fayers P, Bottomley A; EORTC Quality of Life Group; Quality of Life Unit. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. *Eur J Cancer*. 2002 Mar;38 Suppl 4:S125-33.

FDA Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Issued July 2009. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf. Accessed: 11 January 2017.

FDA. The FDA Warns that Biotin May Interfere with Lab Tests: FDA Safety Communication. https://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm586505.htm. Issued November 28, 2017. Accessed August 13, 2018.

Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol*. 2007 Mar;18(3):581-92.

Firmagon (degarelix for injection). Prescribing Information. Ferring Pharmaceuticals Inc., Parsippany, NJ, USA. Revised 07/2016. Available at: http://firmagon.com/. Accessed: 12 January 2017.

Foundation for Promotion of Cancer Research. Cancer Statistics in Japan-2012. December 2012.

Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin*. 2001 Jan-Feb;51(1):15-36.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011 Dec;20(10):1727-36.

Hoare D, Skinner TA, Black A, Robert Siemens D. Serum follicle-stimulating hormone levels predict time to development of castration-resistant prostate cancer. *Can Urol Assoc J*. 2015 Mar-Apr; 9(3-4):122-127.

Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol*. 2006; 24:3984-3990.

Hussain M, Goldman B, Tangen C, et al. Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: data from Southwest Oncology Group Trials 9346 (Intergroup Study 0162) and 9916. *J Clin Oncol*. 2009; 27(15):2450-2456.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013 Sep;22(7):1717-27.

Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2006 Sep 20;24(27):4448-56.

Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int*. 2008 Dec;102(11):1531-8.

Klotz L, O'Callaghan C, Ding K, et al. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. *J Clin Oncol*. 2015 Apr 1;33(10):1151-6.

Kreis W. Current chemotherapy and future directions in research for the treatment of advanced hormone-refractory prostate cancer. *Cancer Invest*. 1995;13(3):296-312.

Lachin J. Biostatistical Methods: The Assessment of Relative Risks. 2nd ed. Balding D, Cressie N, Fitzmaurice G, Johnstone I, Molenberghs G, Scott D, et al., editors: John Wiley & Sons, Inc.; 2010.

Limonata P, Montagnani Marelli M, Moretti RM. LHRH analogues as anticancer agents: pituitary and extrapituitary sites of action. *Expert Opin Investig Drugs*. 2001 Apr;10(4):709-20.

Loblaw DA, Mendelson DS, Talcott JA, et al; American Society of Clinical Oncology. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. *J Clin Oncol*. 2004 Jul 15;22(14):2927-41.

Lopez AM, Pena MA, Hernandez R, Val F, Martin B, Riancho JA. Fracture risk in patients with prostate cancer on androgen deprivation therapy. *Osteoporos Int*. 2005 Jun;16(6):707-11.

Lupron Depot. Prescribing Information. AbbVie Inc., North Chicago, IL, USA. Revised 6/2016. Available at: http://www.lupron.com/prescribing-information.aspx. Accessed: 12 January 2017.

Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. *J Urol*. 2002 Sep;168(3):1005-7.

Prostap 3 DCS. Summary of Product Characteristics, Section 4.8. Takeda UK Ltd. Revised 16/03/2016. Available at: https://www.medicines.org.uk/emc/medicine/24680. Accessed: 12 January 2017.

Proust-Lima C, Taylor JM, Williams SG, et al. Determinants of change in prostate-specific antigen over time and its association with recurrence after external beam radiation therapy for prostate cancer in five large cohorts. *Int J Radiat Oncol Biol Phys*. 2008; 72(3):782-791.

Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS; Urologic Diseases in America Project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer*. 2007 Oct 1;110(7):1493-500.

Schally AV, Coy DH, Arimura A. LH-RH agonists and antagonists. *Int J Gynaecol Obstet*. 1980;18(5):318-24.

Scher HI, Morris MJ, Stadler WM, et al; Prostate Cancer Clinical Trials Working Group. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol*. 2016 Apr 20;34(12):1402-18.

Shore ND. Experience with degarelix in the treatment of prostate cancer. *Ther Adv Urol*. 2013 Feb;5(1):11-24.

Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014 Jan-Feb;64(1):9-29.

Spry NA, Kristjanson L, Hooton B, et al. Adverse effects to quality of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer. *Eur J Cancer*. 2006 May;42(8):1083-92.

Tolis G, Ackman D, Stellos A, et al. Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. *Proc Natl Acad Sci USA*. 1982 Mar;79(5):1658-62.

Tombal B, Miller K, Boccon-Gibod L, et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. *Eur Urol*. 2010 May;57(5):836-42.

Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst*. 2007 Oct 17;99(20):1516-24.

Waxman J, Man A, Hendry WF, et al. Importance of early tumour exacerbation in patients treated with long acting analogues of gonadotrophin releasing hormone for advanced prostatic cancer. *Br Med J (Clin Res Ed)*. 1985 Nov 16;291(6506):1387-8.

Williams SG, Duchesne GM, Millar JL, Pratt GR. Both pretreatment prostate-specific antigen level and posttreatment biochemical failure are independent predictors of overall survival after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2004;60:1082–7.

APPENDICES

Appendix 1. Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Note: Adapted from Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

Appendix 2. EuroQol EQ-5D-5L Questionnaire

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

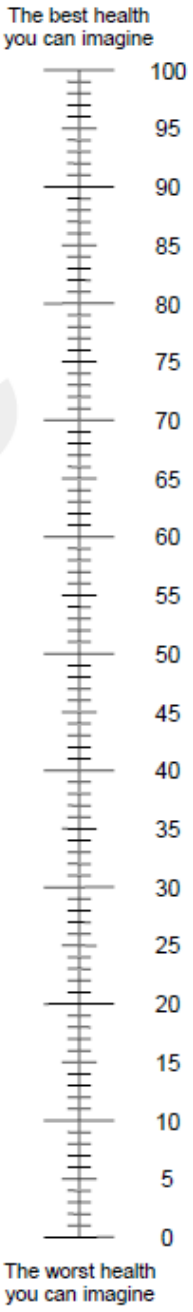
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 3. Quality of Life Questionnaire: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4. Quality of Life Questionnaire: EORTC QLQ-PR25

ENGLISH

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid: Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

ENGLISH

During the last 4 weeks:	Not at all	A little	Quite a bit	Very much
47. Has weight **loss** been a problem for you?	1	2	3	4
48. Has weight **gain** been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS:

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

Appendix 5. Adverse Event Severity Grading

When assessing adverse events, refer to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, June 14, 2010 (available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). A copy of the National Cancer Institute CTCAE table will be provided in the investigator site file.

The National Cancer Institute CTCAE is a descriptive terminology that can be utilized for adverse event reporting. A grading (severity) scale is provided for each adverse event term.

Components and Organization of the National Cancer Institute CTCAE

- System Organ Class (SOC). SOC, the highest level of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy, is identified by anatomical or physiological system, etiology, or purpose (eg, SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, adverse events are listed and accompanied by descriptions of severity (grade).
- CTAE Terms. Each CTCAE term is a MedDRA LLT (Lowest Level Term).
- Definitions. A brief definition is provided to clarify the meaning of each adverse event term.
- Grades. Grade refers to the severity of the adverse event. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each adverse event based on this general guideline:
    - Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
    - Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
    - Grade 4 Life-threatening consequences; urgent intervention indicated; and
    - Grade 5 Death related to adverse event.

      A semi-colon indicates “or” within the description of the grade. A single dash (-) indicates a grade is not available. Not all grades are appropriate for all adverse events. Therefore, some adverse events are listed with fewer than 5 options for grade selection.
- Grade 5. Grade 5 (Death) is not appropriate for some adverse events and therefore is not an option.

Appendix 6. Guidelines for Elevations in Hepatic Enzymes

Study drug treatment should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline. For this purpose, local labs can be used. However, duplicate samples should be taken for central analysis.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld, even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	**Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests[a,b]**
If AST or ALT ≥ 3 x ULN **and** total bilirubin > 2 x ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 x ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions

b. Local labs can be used. However, duplicate samples should be taken for central analysis.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

- Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever);
- Prior and concurrent disease or illnesses;
- Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents;
- Prior and concurrent use of alcohol, recreational drugs, and special diets;
- Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms;
- Physical examination.

Recommended tests:

Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist.

- Repeat liver tests as per Appendix Table 1[a];
- Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests;
- Complete blood count with differential to assess for eosinophilia;
- Serum acetaminophen (paracetamol) concentration;
- Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus;
- Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc;
- Serology for celiac disease;
- Appropriate liver imaging; and
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

Abbreviations: INR, international normalized ratio

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.