CLINICAL STUDY PROTOCOL

Protocol Title:	Relugolix Versus Leuprolide in Patients with Prostate Cancer: A Randomized, Open-Label Study to Assess Major Adverse Cardiovascular Events (REPLACE-CV)
Protocol Number:	MVT-601-056
Compound:	Relugolix
Study Phase:	Phase 3
Short Title:	Randomized Study to Evaluate MACE in Patients with Prostate Cancer Treated with Relugolix or Leuprolide Acetate
Sponsor Name:	[redacted]
Regulatory Agency Identifier Numbers:	IND: 118736
Original:	26 August 2022
Amendment 1:	16 May 2023
Amendment 2:	31 January 2024

SPONSOR SIGNATORY

Relugolix Versus Leuprolide in Patients With Prostate Cancer: A Randomized, Open-Label Study to Reduce Adverse Cardiovascular Events (REPLACE-CV)

Protocol Number: MVT-601-056 Amendment 2

This protocol has been approved by [redacted]. The following signatures document this approval.

Salim Mujais, MD — Date

Senior Vice President, Clinical Research Biopharma

[redacted] — Date

Associate Director, Biostatistics

[redacted] — Date

Director, Safety Evaluation and Risk Management

[redacted] Date

Executive Director, Clinical Research

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 receive the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Principal Investigator Signature
Clinical Site Number	Date

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1.1. Synopsis

Protocol Title: Relugolix Versus Leuprolide in Patients With Prostate Cancer: A Randomized, Open-Label Study to Assess Major Adverse Cardiovascular Events (REPLACE-CV)

Short Title: Randomized Study to Evaluate MACE in Patients with Prostate Cancer Treated with Relugolix or Leuprolide Acetate

Rationale:

Androgen deprivation therapy (ADT) is the foundation of treatment for advanced prostate cancer and is also used as adjuvant treatment in particular men (based on risk category) for primary or salvage radiation therapy. Currently gonadotropin-releasing hormone (GnRH) receptor agonists are the standard of care. One major disadvantage of using an agonist to suppress testosterone is the initial stimulation of the hypothalamus-pituitary-gonadal axis that occurs prior to desensitization and lasts 1 to 3 weeks. This results in a rise in luteinizing hormone and follicle stimulating hormone, a subsequent testosterone surge, and in some men, an increase in clinical symptoms (Oh et al. 2010), including increased bone pain, spinal cord compression, pathologic fracture, bladder outlet obstruction, and even death (Oh et al. 2010). Cardiovascular events also have emerged as an immediate post-treatment concern with GnRH agonists, perhaps due to the hormone surge (Margel et al. 2019; Shore 2020). More recently, GnRH receptor antagonists have been approved for clinical use; relugolix (ORGOVYX®), the first oral GnRH receptor antagonist, was approved on 18 Dec 2020 by the United States Food and Drug Administration (FDA), providing immediate and sustained testosterone suppression. Because GnRH receptor antagonists block hormonal release at the level of the anterior pituitary, they provide immediate testosterone suppression. Moreover, emerging data suggest GnRH receptor antagonists may offer a possible advantage with a lower incidence of major adverse cardiovascular events (MACE) compared with GnRH receptor agonists (Albertsen et al. 2014; Margel et al. 2019; Abufaraj et al. 2020; Davey and Kirby 2020; Shore 2020; Challa et al. 2021). In addition, a recent analysis of events in the FDA Adverse Event Reporting System showed fewer cardiovascular events reported with GnRH receptor antagonists than with GnRH receptor agonists (Zhang et al. 2021). A recent randomized, open-label study (PRONOUNCE) compared the safety of a GnRH receptor antagonist (degarelix) to a GnRH receptor agonist (leuprolide acetate) in patients with advanced prostate cancer and known cardiovascular disease (Lopes et al. 2021). Due to slower than predicted enrollment and the aggregate primary outcome rate (MACE) being lower than expected, study enrollment was terminated, and the results were inconclusive.

In the pivotal phase 3 study MVT-601-3201, treatment with relugolix in advanced prostate cancer was associated with a 54% reduction in the overall risk of MACE, defined as nonfatal myocardial infarction, nonfatal stroke, and death from any cause, versus leuprolide acetate (Shore et al. 2020). Study patients with a history of MACE in the leuprolide acetate group had an almost 5-fold higher odds of having a new MACE compared with those in the relugolix group (odds ratio 5.8 with 95% confidence interval [CI]: 1.5, 23.3) (Shore et al. 2020). There were limitations of the analysis, including that MACE was not defined per current FDA guidance (Hicks et al. 2018), observed MACE was not independently adjudicated, and no inferential

comparisons of MACE between treatment groups were predefined; therefore, the findings in study MVT-601-3201 were hypothesis generating. The phase 3 study MVT-601-056 was designed to characterize the observation of a lower incidence of MACE in patients more aligned with standard practice (less cardiovascular and other exclusions than a traditional study population) treated with relugolix versus those treated with leuprolide acetate. Amendment 1 of the protocol is provided for reference (Appendix 5).

The study was discontinued by the Sponsor. The FDA was notified on 01 Dec 2023, and investigative sites were notified on 04 Dec 2023 to stop enrollment.

This protocol amendment includes a discontinuation phase to allow actively enrolled patients to remain on study medication (up to 12 months) until they are able to transition to standard of care (SOC) to mitigate any interruptions in their cancer treatment.

Objectives and Endpoints

Objective	Endpoint
• To describe the safety of relugolix in the study population	• The safety of relugolix will continue to be assessed in the study population.

Overall Design

The original study was a randomized open-label study to evaluate the risk of MACE in patients with prostate cancer with defined high-risk cardiovascular disease who are appropriate to be treated either with relugolix or leuprolide acetate for a planned duration of 12 months or more. This study was discontinued by the Sponsor on 01 Dec 2023. In an effort to mitigate any treatment interruptions, actively enrolled patients will be allowed to remain on study drug up to a period of 12 months ending Dec 2024 if they choose to remain in the discontinuation phase of the study. During this discontinuation phase, all active investigative sites will be expected to formulate a transition plan for their study patients from this clinical study to SOC as soon as practicable.

The study population includes men ages 18 and older with prostate cancer. Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study or patient safety. Eligibility criteria are described below.

Inclusion Criteria:

1. Was previously enrolled in the original version and amendment 1 of this study
2. Has voluntarily resigned and dated the informed consent form prior to transition to the discontinuation phase of this study

Exclusion Criteria:

Not applicable as patients were previously excluded under the original version and amendment 1.

Disclosure Statement:

This is a randomized study with collection of clinical data at baseline and at follow-up.

Number of Groups: 2

This is an open-label study where no blinding will be applied for the study patients and treatment physician.

Number of Patients:

Approximately 2250 patients (expected to be equally allocated [approximately 1125 patients] between the two treatment groups) will be enrolled. As of 04 Dec 2023, enrollment into this study was stopped. However, patients who have already signed the informed consent will be allowed to complete the randomization process and enroll in the discontinuation phase of the study through the end of Dec 2024, pending eligibility.

Stratification Factors for Treatment Randomization:

- MACE history (yes versus no);
- Age (≤ 65 years old versus > 65 years old);
- Presence or absence of M1 metastatic disease (yes versus no) (metastases in regional lymph node[s] are considered N1 and will, therefore, be stratified as non-metastatic).

These 3 factors will be used for stratifying the randomization.

Intervention Groups and Duration:

Patients will be randomized 1:1 for this study to either relugolix or to leuprolide acetate using permuted block randomization.

As of 04 Dec 2023, patients currently enrolled in this study will be provided with up to a 12-month clinical supply of the randomized study intervention (relugolix or leuprolide acetate) they had been previously assigned. This supply will allow for transition from study treatment to SOC by their health care providers as soon as practicable.

Statistical Methods

Analysis Population

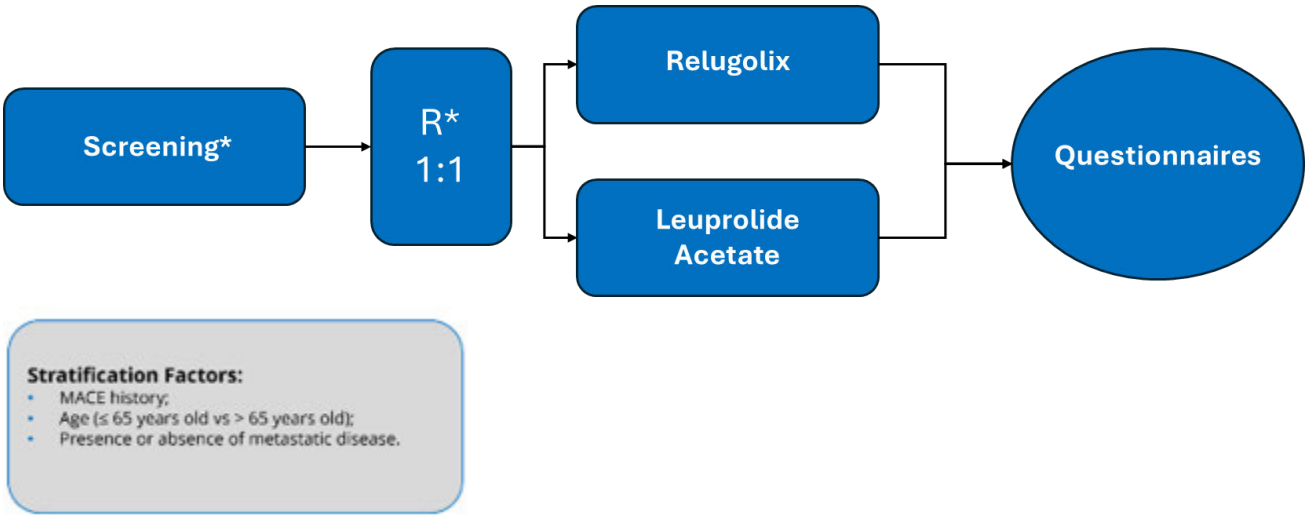
The analysis population is the Safety Population defined as all patients who are randomized into the study with at least 1 dose of study drug.

Sample Size Estimation

As of 04 Dec 2023, enrollment into the study was stopped and no formal statistical analysis will be performed.

1.2. Schema

Figure 1: Study Schema



Abbreviations: MACE = major adverse cardiovascular event; R = randomization.
*Note: Screening and randomization was completed in Dec 2023.

1.3. Schedule of Activities

NOTE: During the discontinuation phase of the study, questionnaires will be collected until early termination/end of study to collect safety information. Other assessments may be performed at the discretion of the Investigator.

Assessment/Procedure	Responsible Party	Screening[a] (28 days before Day 1)	Day 1	Study Treatment Period[b] (Months)					Early Termination/ End of Study[c]
				3	6	9	12	Every 3 Months	
Informed consent	Investigator	X							
Inclusion and exclusion criteria	Investigator	X							
Demographics	Investigator	X							
Physical examination[d]	Investigator	X							
Vital signs[e]	Investigator	X							
Weight and height[f]	Investigator	X							
12-lead ECG	Recruiting physician (if not done within 6 months prior to screening, see Section 8.2.1.3)	X							
Medical history (including detailed prostate cancer history, current prostate cancer disease status and treatment at study entry)	Patient-reported (Baseline questionnaire)	X							
	Recruiting physician								
Family history of cardiovascular disease	Patient-reported (Baseline questionnaire)	X							

Assessment/Procedure	Responsible Party	Screening[a] (28 days before Day 1)	Day 1	Study Treatment Period[b] (Months)					Early Termination/ End of Study[c]
				3	6	9	12	Every 3 Months	
Testosterone	Investigator (if not done within 6 months prior to screening, see Section 8.2.1.4)	X							
	Investigator			6 weeks after start of study treatment, every 6 months thereafter, and at time of PSA rise (Section 8.2.1.4).					
Serum PSA	Investigator (if not done within 6 months prior to screening, see Section 8.2.1.4)	X							
Baseline questionnaire	Patient-reported	X							
PROMIS Short Form V2.0 – Cognitive Function 8a[g]	Patient-reported	X		Every 12 months on study.					
Randomization	Investigator		X						
Study intervention administration: leuprolide acetate or relugolix[h]	Investigator		X[i]	Administered as per label.					
Standard of care visit[j]	Investigator			X	X	X	X	X	X[c]
Follow-up questionnaires[k]	Patient-reported			X	X	X	X	X	X
Early discontinuation / End of study questionnaire	Patient-reported								X

Assessment/Procedure	Responsible Party	Screening[a] (28 days before Day 1)	Day 1	Study Treatment Period[b] (Months)					Early Termination/ End of Study[c]
				3	6	9	12	Every 3 Months	
Selective safety data[l]	Patient-reported (Follow-up questionnaire)	X		X	X	X	X	X	X
	Investigator		X (see Section 8.3)						
Concomitant medications[m]	Investigator	X							
	Patient-reported (Follow-up questionnaire)	Patient-reported		X	X	X	X	X	
Drug accountability	Clinical trial supply vendor (or designee)			X	X	X	X	X	X

Abbreviations: CRO = clinical research organization; ECG = electrocardiogram; eCRF = electronic case report form; PSA = prostate-specific antigen.

[a] Recruiting and screening will be completed by the study centers. Study centers will educate, set the study expectations, and obtain informed consent from study patients. Informed consent forms will include permission for study data to be collected, analyzed, and for contacts to be made by the CRO study team at specific time-intervals during follow-up for the collection of study information. Each patient will also be asked to provide information regarding alternative contacts (eg, close relatives or friends, or primary care physician or cardiologist). If the CRO cannot reach the patient or relatives after several attempts, they will contact the patient's primary care physician/cardiologists/attending physician(s).

[b] Patient's responses will be collected (every 3 months) via an electronic questionnaire (or phone calls or other methods if the patient and family member are unable to complete the questionnaire electronically). The questionnaires will be collected until the end of study. Patients will be instructed to consult with the principal investigator if they do not have access to a phone or an electronic device. Note: Other assessments may be performed (in clinic or telehealth) per investigator's discretion during the discontinuation phase of study, but are no longer required.

[c] Can be performed in clinic or telehealth as standard of care begins.

[d] A complete physical examination will be performed (see Section 8.2.1.1).

[e] Vital signs will be measured in a seated position after 5 minutes rest and will include oral temperature, pulse rate, and systolic and diastolic blood pressure. Two readings of blood pressure will be taken and averaged.

[f] Body mass index will be calculated based on weight and height.

[g] Potential decline in cognitive function as seen on follow-up will be discussed by the medical monitor and investigator.

[h] Relugolix will be mailed to patients.

[i] The investigator must record all dates of leuprolide acetate administration in the electronic data capture (EDC) system. For the relugolix group, patients will self-administer relugolix at home. The investigator must call the patient to confirm the date that the patient first started taking relugolix and record this date in EDC.

[j] Can be either in office or by telehealth, performed as needed per investigator discretion.

[k] Data collected during the discontinuation phase of the study will focus on the clinical status of the prostate cancer and therapy, concomitant medications, hospitalizations for any reason, emergency room visits, adverse events (serious adverse events or adverse events resulting in discontinuation of study drug) and change in cardiovascular risk factors. If the patient does not react to the e-mail-based follow-up questionnaire alerts, phone contacts with the study patients can be established as a reminder.

[l] Selective safety data collected in this study will include serious adverse events and nonserious adverse events that lead to the discontinuation of relugolix or leuprolide acetate.

[m] All concomitant medications currently being taken or were used by the patient within 30 days prior to signing the ICF will be recorded at baseline by the recruiting physician and reviewed by the study medical monitor and CRO. During the discontinuation phase of the study, new concomitant medications will be reported by patients via the email-based follow-up questionnaire.

2. INTRODUCTION

Relugolix (previously known as T-1331285, TAK-385 and RVT-601, also known as MVT-601) is an orally active, nonpeptide, gonadotropin-releasing hormone (GnRH) receptor antagonist developed as an oral 120-mg dose to induce sustained testosterone suppression to levels < 50 ng/dL for the treatment of men with advanced prostate cancer. Relugolix (ORGOVYX®) was approved for the treatment of adult patients with advanced prostate cancer on 18 Dec 2020 in the United States (ORGOVYX [relugolix] United States Prescribing Information [USPI] 2023). Amendment 1 of the protocol is provided for reference (Appendix 5).

2.1. Background

Cardiovascular disease is a leading cause of death in men with advanced prostate cancer (Sturgeon et al. 2019; Leong et al. 2020). This is likely due to recent progress in early diagnosis and effective treatment, which lengthens the survival time of men with advanced prostate cancer and increases the likelihood that they will die of other causes (Epstein et al. 2013). It also has been shown that men with advanced prostate cancer have a higher risk of cardiovascular disease than those with localized disease, although the reasons for this are not entirely clear.

Men with prostate cancer have a baseline higher risk of developing cardiovascular disease, and this risk increases with the use of GnRH receptor agonists (Keating et al. 2010). Studies have also found a higher risk of major adverse cardiovascular events (MACE) in patients with prostate cancer treated with GnRH receptor agonists compared with GnRH receptor antagonists, particularly in men with preexisting cardiovascular disease (Saigal et al. 2007; Keating et al. 2010; Margel et al. 2019).

Challa and colleagues reviewed the current medical literature to compare cardiotoxicity of GnRH receptor antagonists and GnRH receptor agonists and identified more cardiovascular events in patients using GnRH receptor agonists than those using GnRH receptor antagonists, especially among patients with preexisting cardiovascular disease (Challa et al. 2021).

Despite the literature evidence available in the last years from different type of studies (randomized controlled, observational, and meta-analyses), GnRH receptor agonists remain the standard of care for men requiring androgen deprivation therapy (ADT) for advanced prostate cancer. Furthermore, although guidelines on use of ADT in prostate cancer do highlight the need for screening and intervention to prevent/treat diabetes and cardiovascular disease, there is no recommendation for any particular type or class of ADT (Schaeffer et al. 2021). Currently GnRH receptor agonists are the standard of care. One major disadvantage of using an agonist to suppress testosterone is the initial stimulation of the hypothalamus-pituitary-gonadal axis that occurs prior to desensitization and lasts 1 to 3 weeks. This results in a rise in luteinizing hormone and follicle stimulating hormone, a subsequent testosterone surge, and in some men, an increase in clinical symptoms (Oh et al. 2010), including increased bone pain, spinal cord compression, pathologic fracture, bladder outlet obstruction, and even death (Oh et al. 2010). Cardiovascular events also have emerged as an immediate post-treatment concern with GnRH agonists, perhaps due to the hormone surge (Margel et al. 2019; Shore 2020).

Since 2010, the Food and Drug Administration (FDA) has required that the risk of cardiovascular disease be included in the safety information for GnRH receptor agonists. Eligard® and Lupron Depot® labeling include a warning of an increased risk of myocardial

infarction, sudden cardiac death, and stroke associated with use of GnRH receptor agonists in men and recommend that patients be monitored for symptoms and signs suggestive of development of cardiovascular disease (Eligard USPI 2019; Lupron Prescribing Information 2019). The increased risk associated with the use of GnRH receptor agonists is hypothesized to occur in two distinct timeframes. An early increase in cardiovascular risk has been described in men with preexisting cardiovascular disease, possibly from plaque rupture and resultant thrombosis, whereas a later increase in risk may occur from the resulting hypogonadal state with an increase in central obesity, insulin resistance, hypertension, and hyperlipidemia (Albertsen et al. 2014; Crawford et al. 2017; Margel et al. 2019).

The medical literature has shown that one major potential difference between the GnRH receptor agonists and GnRH receptor antagonists is a possible advantage for GnRH receptor antagonists regarding MACE, with most of the data demonstrating a lower incidence of MACE with the GnRH receptor antagonists (Albertsen et al. 2014; Margel et al. 2019; Abufaraj et al. 2020; Davey and Kirby 2020; Shore 2020; Challa et al. 2021). A recent randomized, open-label study (PRONOUNCE) compared the safety of a GnRH receptor antagonist (degarelix) to a GnRH receptor agonist (leuprolide acetate) in patients with advanced prostate cancer and known cardiovascular disease (Lopes et al. 2021). Due to slower than predicted enrollment and lower rate of MACE, study enrollment was terminated and the results were inconclusive. In addition, a recent analysis of events in the FDA Adverse Event Reporting System showed fewer cardiovascular event reporting with GnRH receptor antagonists than with GnRH receptor agonists (Zhang et al. 2021). Additionally, the American Heart Association recently published a consensus statement describing the risks associated with specific hormonal therapies used to treat breast and prostate cancer and provides an evidence-based approach to prevent and detect adverse cardiovascular outcomes (Okwuosa et al. 2020).

2.2. Study Rationale

In the pivotal phase 3, randomized, open-label, parallel group study to evaluate the safety and efficacy of relugolix in men with advanced prostate cancer, MVT-601-3201, treatment with relugolix was associated with a 54% reduction in the overall risk of MACE, defined as nonfatal myocardial infarction, nonfatal stroke, and death from any cause, versus leuprolide acetate (Shore et al. 2020). Study patients with a history of MACE in the leuprolide acetate group had an almost 5-fold higher odds of having a new MACE compared with those in the relugolix group (odd ratio 5.8 with 95% confidence interval [CI]: 1.5, 23.3) (Shore et al. 2020). There were limitations of the analysis, including that MACE was not defined per current FDA guidance (Hicks et al. 2018), observed MACE was not independently adjudicated, and no inferential comparisons of MACE between treatment groups were predefined.

The findings in study MVT-601-3201 were hypothesis generating, and SMPA proposed to further characterize the observation of lower MACE in patients treated with relugolix in study MVT-601-056. This proposed study is a randomized, open-label study of patients treated with either relugolix or leuprolide acetate for prostate cancer or as an adjunct to primary or salvage radiation therapy, with a treatment plan to be on at least 12 months of continuous ADT. This study planned to generate data by enrolling a population with higher cardiovascular risks and histories of cardiovascular disease than the population in oncology studies such as MVT-601-3201.

As of 04 Dec 2023, enrollment in the MVT-601-056 study was halted and no cardiovascular events will be adjudicated. The study will remain active for patients currently enrolled in this study to mitigate any treatment interruptions and allow sufficient time for investigators to transition their study patients to standard of care (SOC). In this discontinuation phase, patients will be provided with up to a 12-month clinical supply of the randomized study intervention (relugolix or leuprolide) they had been previously assigned.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of relugolix may be found in the investigator's brochure (version 14.1; dated 16 Dec 2022) and Package Insert (ORGOVYX [relugolix] USPI 2023). The risk assessment and mitigation strategies are outlined in Section 2.3.1.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention		
Loss of Bone Mineral Density	Loss of bone mineral density can be a consequence of androgen deprivation therapy. In phase 2 prostate cancer studies, dual-energy x-ray absorptiometry was performed at baseline and end of study treatment. Mild loss of bone mineral density in the range associated with medical castration (-1 to -3%) was observed after 24 or 48 weeks (no apparent difference with longer treatment duration) of treatment with relugolix. No increased risk of fracture has been observed. In the primary analysis population of the phase 3 advanced prostate cancer study, MVT-601-3201, bone health events (including fracture-related adverse events and osteopenia-related terms) were reported for similar proportions of patients in both the relugolix (3.2%) and leuprolide groups (3.9%).	In the prostate cancer program, routine monitoring of serious adverse events, including fractures, will continue. Use of anti-resorptive bone therapy, such as bisphosphonates or denosumab, may be considered by the investigator.
QTc Prolongation	In cardiovascular safety pharmacology studies, relugolix inhibited hERG channel current at concentrations of ≥ 3 µg/mL, with a concentration producing 50% inhibition of 9.7 µg/mL (15.6 µM). QT prolongation that was not clinically significant occurred in Study C27001. There was no apparent relationship observed between relugolix concentration and QTc interval duration, and the QTc changes were	In completed thorough QT/QTc study TAK-385_106, single oral doses of relugolix (60 and 360 mg) administered to healthy adults did not prolong QT/QTc interval; however, QTc prolongation is retained as a potential

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	attributable to the class-related suppression of testosterone. Results of study TAK-385_106, designed to determine the effects of relugolix relative to placebo on QTcF interval prolongation as the measure of cardiac repolarization following single oral doses in healthy patients, showed that administration of single doses of relugolix 60 or 360 mg in patients did not prolong QT/QTc intervals. In the primary analysis population of the phase 3 advanced prostate cancer study, MVT-601-3201, adverse events related to QTc prolongation were reported for similar proportions of patients in the relugolix (2.1%) and leuprolide (1.9%) groups. No clinically meaningful direct effects on QTc intervals have been observed in clinical studies of relugolix.	risk associated with class effect of drugs associated with androgen deprivation. Patients with a baseline QTcF > 470 msec will be excluded. Patients will be informed of the signs and symptoms of QT prolongation as per approved labeling for the product(s) and advised to contact the study doctor/staff immediately for signs or symptoms of QT prolongation. ECGs will be obtained as per clinical judgment of the investigator.
Hepatic Transaminase Elevations	Overall, across the relugolix program, there have been asymptomatic reversible elevations in hepatic transaminases, some resulting in study medication discontinuation. Patterns of elevations vary, and no clear dose-response relationship is evident. No cases meeting Hy's law criteria have been reported. Based on clinical observations, hepatic transaminase elevations are considered a potential risk of relugolix.	Periodic monitoring of liver tests, per investigator judgment, with implementation of appropriate management, where applicable.
Carbohydrate and Lipid Metabolic Effects	The class effects of GnRH receptor antagonists include metabolic and cardiovascular changes that have been reported in patients treated with these agents, particularly men treated for prostate cancer (diabetes mellitus, dyslipidemia, and weight gain) and are stated among the potential risks for patients taking relugolix. Reduction in testosterone levels, and perhaps estrogen levels, is associated with decreased insulin sensitivity. Metabolic changes are not necessarily severe; however, the impact on cardiovascular disease may result in serious outcomes, particularly for elderly men. In the primary analysis population of the phase 3 advanced prostate cancer study, MVT-601-3201, data showed abnormalities of certain laboratory parameters observed over a 48-week treatment period with	Periodic monitoring of blood glucose and/or HbA1c, lipid levels, and weight, per investigator judgment with implementation of appropriate treatments and preventive measures, where applicable, in patients receiving long-term treatment with relugolix monotherapy is warranted.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	relugolix, including those associated with physiologic consequences of testosterone suppression. These included: increase in fasting serum glucose concentrations > 200 mg/dL and greater than baseline (relugolix 7.4%; leuprolide 13.0%), increase in hemoglobin A1c (HbA1c) (relugolix 0.31%, leuprolide 0.26%) and HbA1c ≥ 1.0% from baseline (relugolix 7.2%; leuprolide 6.8% [baseline median HbA1c 5.70 in both groups]), and increase in cholesterol concentrations > 200 mg/dL and greater than baseline (relugolix 48.9%; leuprolide 44.2%).	

Abbreviations: ECG = electrocardiogram; GnRH = gonadotropin-releasing hormone; HbA1c = hemoglobin A1c; hERG = human Ether-à-gogo-related gene; QTc = QT (interval) corrected for heart rate; QTcF = QT interval corrected for heart rate using Fridericia's formula.

2.3.2. Benefit Assessment

Treatment with relugolix may offer the potential benefit of MACE risk reduction compared to leuprolide acetate in patients with prostate cancer. As of 04 Dec 2023, enrollment into this study was stopped and currently enrolled patients may continue to receive clinical drug supply until they transition to SOC. The safety of relugolix will continue to be assessed in the study population.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to patients in this study, the potential risks identified in association with relugolix are justified by the anticipated benefits that may be afforded to patients with prostate cancer.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoint
• To describe the safety of relugolix in the study population	• The safety of relugolix will continue to be assessed in the study population.

4. STUDY DESIGN

4.1. Overall Design

The original design was a randomized study to evaluate the risk of MACE for relugolix compared with leuprolide acetate. The study was intended to collect clinical and cardiovascular risk factor data on patients ages 18 and older who were receiving relugolix or leuprolide acetate for their prostate cancer or as adjunct to radiation therapy with a treatment plan to be on at least 12 months of continuous ADT. Amendment 1 of the protocol is provided for reference (Appendix 5).

This study was discontinued by the Sponsor on 01 Dec 2023, in an effort to mitigate any treatment interruptions, actively enrolled patients will be allowed to remain on study drug up to a period of 12 months ending Dec 2024. During this discontinuation phase, all active investigative sites will be expected to formulate a transition plan for their study patients from this clinical study to SOC as soon as practicable. This protocol has been modified to account for the shift to a discontinuation phase study.

4.2. Scientific Rationale for Study Design

The medical literature and FDA Adverse Event Reporting System data (Zhang et al. 2021), as well as results from the pivotal study MVT-601-3201, suggest that one major potential advantage of a GnRH receptor antagonist, such as relugolix, is a lower incidence of MACE than that observed with GnRH receptor agonists.

The study was discontinued by the Sponsor and the FDA was notified on 01 Dec 2023. Time to first MACE will not be assessed during the discontinuation phase of the study. Therefore, the scientific rationale for this study design no longer applies.

4.3. Justification for Dose

The recommended dosing regimen for relugolix is a single 360-mg loading dose (3 × 120-mg tablets) taken orally, followed by a 120-mg dose (1 × 120-mg tablet), taken orally, once daily; in the event that in addition to the relugolix the patient requires a combined P-glycoprotein (P-gp) inducer and strong CYP3A inducer, relugolix dosing will be the same single 360 mg loading dose followed by 240 mg dose daily (ORGOVYX [relugolix] USPI 2023). Leuprolide acetate 3-M or 6-M depot injection (per the investigator's judgement) was selected as the active comparator.

As of 04 Dec 2023, patients currently enrolled in this study will be provided with up to a 12-month clinical supply of the randomized study intervention (relugolix or leuprolide acetate) they had been previously assigned. This clinical supply is intended to mitigate any interruptions in treatment and to allow sufficient time for patients to transition from study treatment to SOC by their health care providers as soon as practicable.

4.4. End of Study Definition

The end of study is defined as the date of the last dispensation (last injection of leuprolide; last delivery of relugolix) before the patient transitions to SOC treatment.

5. STUDY POPULATION

The study population includes men ages 18 and older with prostate cancer.

5.1. Inclusion Criteria

A patient will be eligible for inclusion in the discontinuation phase of the study if the following applies:

1. Was previously enrolled in the original version and amendment 1 of this study
2. Has voluntarily resigned and dated the informed consent form prior to transition to the discontinuation phase of this study

5.2. Exclusion Criteria

Not applicable as patients were previously excluded under the original protocol.

5.3. Screen Failures

Enrollment into this study was stopped as of 04 Dec 2023, and screen failures are no longer applicable. However, patients who have already signed the informed consent were allowed to complete the randomization process and enroll in the discontinuation phase of the study through the end of Dec 2024, pending eligibility.

6. STUDY INTERVENTION

The study interventions are relugolix and leuprolide acetate.

6.1. Study Interventions Administered

Patients enrolled in this study were randomized 1:1 to receive oral relugolix 120 mg once daily with a loading dose of 360 mg on Day 1, or either leuprolide acetate 22.5 mg 3-M depot or 45 mg 6-M injection (plus first-generation anti-androgen for the first 4 weeks or longer if indicated in the opinion of the investigator).

As of 04 Dec 2023, enrollment in the MVT-601-056 study was halted and actively enrolled patients will be provided up to a 12-month clinical supply (relugolix or leuprolide acetate) based on their randomization assignment if they choose to remain in the discontinuation phase of the study. Amendment 1 of the protocol is provided for reference (Appendix 5).

Table 1: MVT-601-056 Study Interventions

Intervention Name	Relugolix	Leuprolide acetate 3-M or 6-M depot[a] or Leuprolide acetate injectable emulsion
Type	Drug	Drug
Dose Formulation	Tablet	Depot formulation
Dosage Levels	Loading dose: 360 mg (3 × 120 mg) Daily dose: 120 mg (1 × 120 mg)	22.5 mg or 45 mg (or 42 mg injectable emulsion)
Route of Administration	Oral	Subcutaneous or intramuscular
Use	Investigational medicinal product	Active comparator
Sourcing	Relugolix will be sourced and shipped direct-to-patient via a central pharmacy.	Leuprolide acetate will be sourced by the site to the patients.
Packaging and Labeling	Relugolix is provided in a bottle. Each bottle will be packaged and labeled as required for clinical study use.	Leuprolide acetate 22.5 mg 3-M or 45 mg 6-M depot injection used with standard of care packaging and labeling.

[a] If an investigator prefers another dose regimen of leuprolide acetate this will require approval by the medical monitor.

6.2. Preparation/Handling/Storage/Accountability

Relugolix 120-mg tablets will be supplied to the patient in 45-count high-density polyethylene bottles with induction seal, child resistant cap and desiccant. Moreover, patients will be advised to store relugolix at room temperature in a secure location, out of reach of children. Leuprolide acetate (either 22.5 mg 3-M or 45 mg 6-M) depot injection will be provided per standard of care use. It is up to the site to decide which formulation of leuprolide acetate to use for this trial.

Drug accountability of relugolix will be assessed using pill counting done at a return depot by a clinical trial supply vendor (or designee). Each patient will be required to send all empty and/or partially empty bottles of study drug to the return depot at pre-defined intervals for drug accountability at the end of their 12-month transition to SOC treatment.

6.3. Randomization and Stratification

Eligible patients were assigned to one of two treatment groups in accordance with the randomization schedule using an Interactive Response Technology System. At baseline prior to the start of study intervention administration, each patient was randomized in Interactive Response Technology in a 1:1 ratio to one of 2 treatment groups (see Table 2).

Table 2: MVT-601-056 Treatment Arms

Treatment Arm	Randomized Treatment
Group A	Relugolix 360 mg (three 120 mg tablets) single oral loading dose on Day 1 followed by 120 mg orally once daily
Group B	Leuprolide acetate, 22.5 mg 3-M depot injection or Leuprolide acetate, 45 mg 6-M depot injection

Randomization was centrally stratified by the following factors using a permuted block method (see Section 4.1 for further details on the factors):

- MACE history (yes versus no);
- Age (≤ 65 versus > 65 years old);
- Presence of metastatic prostate cancer (yes versus no) (metastases in regional lymph node[s] are considered N1 and will, therefore, be stratified as non-metastatic).

6.4. Study Intervention Compliance

Following randomization, patients will follow SOC practices with their investigator, which for the leuprolide acetate group will include visits for injection of leuprolide acetate. The investigator must record all dates of leuprolide acetate administration in the electronic data capture system. For the relugolix group, patients will self-administer relugolix at home

Each patient will have a follow-up visit (either in office or by telehealth; per the investigator's discretion) during this discontinuation phase until they transition to SOC.

6.5. Concomitant Therapy

All concomitant medications currently being taken or were used by the patient within 30 days prior to signing the informed consent form (ICF) will be recorded at baseline by the recruiting physician and reviewed by the study medical monitor and Clinical Research Organization (CRO). During the discontinuation phase of the study, new concomitant medications will be reported by patients via the follow-up questionnaire. At a minimum, the drug name, start date, and stop date will be recorded.

Patients with prostate cancer disease progression during the discontinuation phase should be managed according to their physician's clinical judgement and individual clinical management plan. Additional treatment for prostate cancer will be recorded as concomitant medication.

6.5.1. Permitted Medications

Patients may be treated with multiple approved prostate cancer medications (ie, enzalutamide, abiraterone acetate, apalutamide, darolutamide, docetaxel, etc.) if it is appropriate in the opinion of the investigator.

6.5.2. Permitted Therapies

A short course of radiotherapy (SBRT) can be used in patients with metastatic disease.

6.5.3. Prohibited Medications

Co-administration of relugolix 120 mg with oral P-gp inhibitors should be avoided. If co-administration is unavoidable, relugolix 120 mg should be taken first, then wait at least 6 hours before taking the P-gp inhibitor (ORGOVYX (relugolix) USPI 2023). Treatment with relugolix 120 mg may be interrupted for up to two weeks if a short course of treatment with a P-gp inhibitor is required. If treatment with relugolix is interrupted for more than 7 days, resume administration of relugolix with a 360 mg loading dose on the first day, followed by 120 mg once daily.

If co-administration with combined P-gp and strong CYP3A inducers is unavoidable, increase the relugolix dose to 240 mg once daily. After discontinuation of the combined P-gp and strong CYP3A inducer, resume the recommended dose of 120 mg relugolix once daily (ORGOVYX (relugolix) USPI 2023).

6.6. Dose Modifications

In general, no modifications to the dose or dosing regimen of relugolix are permitted (ORGOVYX (relugolix) USPI 2023). For the management of oral P-gp inhibitors OR combined P-gp and strong CYP3A inducers when concomitant use cannot be avoided, refer to Section 6.5.3. Of the approved prostate cancer drugs, apalutamide is a known combined P-gp and strong CYP3A inducer and requires dose adjustment outlined in Section 6.5.3.

6.7. Intervention after the End of the Study

Patients may continue receiving relugolix or leuprolide acetate after the end of study if prescribed by their physician per SOC. Post-study treatment with relugolix or leuprolide acetate will not be supplied by the Sponsor.

7. PATIENT DISCONTINUATION/WITHDRAWAL

7.1.1. Temporary Discontinuation

At the discretion of the investigator, study drug can be held for a period of up to 14 consecutive days for evaluation and treatment of an adverse event. Patients may be rechallenged per the investigator's discretion, ending Dec 2024. If treatment with relugolix is interrupted for more than 7 days, resume administration of relugolix with a 360 mg loading dose on the first day, followed by 120 mg once daily. Active sites will receive clinical drug supply until all patients transition to SOC.

7.2. Patient Discontinuation/Withdrawal from the Study

- A patient may withdraw from the study at any time at his own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, an early termination questionnaire should be completed, as shown in the SoA (see Section 1.3).
- The patient may be permanently discontinued from the study at that time.
- If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he repeatedly fails to complete the scheduled questionnaires and is unable to be contacted by the CRO or designee.

7.4. Patient and Study Completion

For an individual patient, study completion is defined as their last study communication at the end of the study (including any follow-up visits or telephone contact for determination of resolution of an adverse event).

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- Per investigator's discretion, repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples. To ensure symmetry of patient contact, all patients will be seen at least every 3 months per investigator's discretion. This visit can be for injection of leuprolide acetate or in person office visit or telehealth visit.

8.1. Efficacy Assessments

There are no efficacy assessments for this study.

8.2. Safety Assessments

Study assessments of safety include serious adverse events, nonserious adverse events leading to discontinuation of relugolix or leuprolide acetate (Section 8.3), and clinical laboratory tests as obtained per standard of care (Section 8.2.1.4). Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Patient Questionnaires

Patients completed a baseline questionnaire at screening (within 28 days before Day 1) and will be expected to complete study questionnaires every 3 months while on study, including during the discontinuation phase. The patient will also be asked to complete an early discontinuation questionnaire upon transition from the study to SOC.

To assess cognition of patients during the study, they will also complete the PROMIS® Short Form V2.0 – Cognitive Function 8a form at baseline and every 12 months. This validated form assesses the frequency of cognitive difficulties experienced in the past 7 days, by asking 8 questions that are evaluated by the sponsor. If a patient's test score is between the 25th and 75th percentile, it reflects typical cognition. Scores at or below the 16th percentile (ie, 1 standard deviation below the mean) are likely to be clinically meaningful and the investigator will be notified for further follow-up of the patient and a discussion of possibly having additional family members assist the patient with completion of the questionnaires. Alternatively, the investigator may be the one to notice there has been a change in cognition with the patient, and a discussion with the medical monitor must occur. If a patient can no longer complete study questionnaires due to new cognitive difficulties, a caregiver or family member can complete the form. However, if the study becomes too challenging for the family and there are no further accommodations available, the patient may be discontinued from the trial.

Potential decline in cognitive function as seen on follow-up must be discussed by the medical monitor and investigator.

Patients are not expected to complete study questionnaires after transition to SOC.

Note: The following assessments may be performed via Table 1 (in clinic or telehealth) per investigator's discretion during the discontinuation phase of study but are no longer required.

8.2.1.1. Physical Examinations

A complete physical examination will be done at screening visit and will include, at a minimum, assessments of the head, ears, eyes, nose, mouth, thyroid, skin, heart and lungs, lymph nodes, genitourinary, gastrointestinal, skeletal, and neurological systems. Height and weight will also be measured and recorded. Body mass index will be calculated based on weight and height.

8.2.1.2. Vital Signs

Vital signs will be measured at screening visit in a seated position after 5 minutes rest and will include oral temperature, pulse rate, and systolic and diastolic blood pressure. Two readings of blood pressure will be taken and averaged.

8.2.1.3. Electrocardiograms

If a patient has had an electrocardiogram (ECG) within 6 months of enrollment, it must be submitted with the eligibility review form (ERF). Otherwise, a single 12-lead ECG will be obtained at the screening visit by the treating physician, the primary care physician, or other qualified healthcare provider as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals and submitted with the ERF.

8.2.1.4. Clinical Safety Laboratory Assessments

If a patient has not had a testosterone level assessed six months prior to screening, then a testosterone level must be obtained from a local laboratory and submitted with the ERF. Testosterone levels also should be obtained and submitted 6 weeks after the first dose of either relugolix or leuprolide acetate and then every 6 months that the patient remains in the trial. Testosterone levels also should be obtained and submitted when a patient has a rising prostate-specific antigen (per the investigator's judgement). Testosterone levels are being checked to make sure that the patient is in the castrate range. A testosterone concentration above the castrate level (≥ 50 ng/dL) requires evaluation. Specifically, the investigator should first determine whether the patient is compliant with their medication; if compliant, additional evaluation should include repeat measurement of serum testosterone. Given the potential for variability with immunoassays, consider evaluation of testosterone using a liquid chromatography tandem mass spectrometry (LC-MS/MS) assay. If upon repeat testing the patient has persistently elevated testosterone above the castrate threshold, a discussion with the medical monitor should occur.

8.3. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative) using the questionnaires. The CRO is responsible for checking the questionnaires for selective safety data

(ie, serious adverse events and nonserious adverse events leading to treatment discontinuation) and for recording, reporting, and following up of these events.

Selective safety data will also be reported by the investigator.

All serious adverse event reporting is conducted in accordance with the Code of Federal Regulations Title 21 312.32.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All adverse events and serious adverse events reported in the follow-up questionnaires will be collected from the signing of the ICF until the final study visit at the time points specified in the SoA (Section 1.3), irrespective of a causal relationship.

For serious adverse events and nonserious adverse events leading to treatment discontinuation reported in the follow-up questionnaires, the CRO is responsible to ensure these selective safety data are recorded and reported to the sponsor (or designee) within 5 calendar days of receipt unless there are suspected unexpected fatal or life-threatening serious adverse reaction reports, in which case they will be reported to the sponsor or designee within 2 business/3 calendar days, whichever is shorter, as indicated in Appendix 2. The CRO will also submit any updated selective safety data to the sponsor as indicated in Appendix 2.

8.3.1.1. Investigator Reporting of Adverse Events and Serious Adverse Events

For serious adverse events reported directly to the investigator, the investigator must submit these selective safety data within 24 hours of site awareness to the sponsor (or designees). Nonserious adverse events leading to treatment discontinuation will be captured in electronic data capture and must be entered within 8 calendar days of site awareness.

Investigators are not obligated to actively seek serious adverse event information after conclusion of the study participation. However, if the investigator learns of any serious adverse events, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Potential adverse events including serious adverse events are recorded by patients in the follow-up questionnaires. All selective safety data fulfilling the minimum criteria for reporting will be sent by the CRO to the sponsor (or designee).

Adverse events and serious adverse events may also be reported by the patient (or caregiver, surrogate, or patient's legally authorized representative) directly to the recruiting physician. If the physician becomes aware of any serious adverse events or nonserious adverse events leading to treatment discontinuation, the recruiting physician is responsible for reporting the selective safety data to the sponsor (or designee).

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse events are provided in Appendix 2.

Care will be taken not to introduce bias when detecting serious adverse events.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After an initial adverse event or serious adverse event report(s), the CRO will undertake steps to validate events as reported by the patient in the follow-up questionnaires. The aim of the event validation procedure is to assemble medical documentation to examine and confirm the event. This may include recontacting the patient to obtain discharge summaries and medical records and/or contacting the investigator. In addition, the electronic medical records of the patient will be retrieved. All medical documentation will be assembled into a clinical dossier and where required, reported to the sponsor.

All serious adverse events will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 2.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Drug Experiences

Swift notification by the CRO to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Expedited safety reports must be prepared for reporting of suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an expedited safety report describing a suspected unexpected serious adverse reaction event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will review and then file it with the investigator brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy in Female Partners of Male Patients

The male patient should report a pregnancy in his female partner.

Details of all partner pregnancies in female partners who become pregnant (estimated date of conception) during the study or within 2 weeks after the last dose of relugolix 120 mg or 3 months after the last dose of leuprolide acetate 22.5 mg 3-M or 6 months after the last 45 mg 6-M depot injection will be collected after the start of study intervention if the female partner agrees to provide information through a Release of Information form.

If a partner pregnancy is reported, the investigator should inform the sponsor (or designee) within 8 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 3.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6. Safety Management Plan

Further detailed information on reporting of serious adverse events and nonserious adverse events leading to treatment discontinuation is included in the safety management plan. The safety management plan shall set forth rules and procedures concerning pharmacovigilance reporting and shall supersede all prior pharmacovigilance and safety agreements.

The CRO will not monitor the sponsor's regulatory reporting obligations to the Health Authorities.

8.4. Treatment of Overdose

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

For this study, any dose of relugolix greater than the daily dose of relugolix 120 mg following the 360-mg loading dose, or 240 mg per day as part of dose modification when relugolix is combined with P-gp and strong CYP3A inducers, will be considered an overdose. There is no known antidote for an overdose.

Refer to product labelling for leuprolide acetate in the event of an overdose.

The investigator reports overdose events to the CRO within 8 calendar days of awareness; the CRO reports overdoses to the sponsor (or designee) with 5 days of awareness, respectively, according to Appendix 2, whether or not the overdose is associated with an adverse event.

The quantity of the excess dose as well as the duration of the overdose should be documented in the Overdose electronic case report form (eCRF).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the patient.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity will not be evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal primary and secondary analysis for this study will be performed.

9.2. Analysis Populations

Safety population is defined as all randomized patients who are treated with at least one dose of relugolix or one injection of leuprolide acetate after the date of randomization to the study. Safety population will be used to analyze other safety data including treatment-emergent adverse events and clinical laboratory tests as obtained per standard of care.

9.3. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. The adverse event analysis will be elaborated in the statistical analysis plan, all other baseline data will be collected and will be listed.

9.3.1. General Considerations

All statistical analyses will be conducted using SAS® Version 9.4 or higher.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the investigational review board (IRB)/independent ethics committee (IEC) before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

- Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- Patients can sign a paper ICF to be eligible for the discontinuation phase of the study. Electronic informed consent (eConsent) will not be available.
- The medical record must include a statement that written informed consent was obtained to allow the patient to continue in the discontinuation phase and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study. Re-consent must occur through the paper ICF consent.
- A copy of the paper ICF(s) must be provided to the patient and the patient's legally authorized representative and the investigator will maintain the signed original document within the patient's record file per local requirements.
- For patients who consented to prior versions of the protocol via eConsent, a copy of the electronic ICF(s) will be available to the patient to review and print a copy via the secure portal.
- The investigator will also fully document the informed consent process in the patient's source records.
- Due to the study entering into a discontinuation phase, all enrolled patients will need to be reconsented.

Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent
- The patient must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins. Results will be posted as per local country requirements.

Data Quality Assurance

This study will be monitored by the sponsor (or designee) in accordance with current GCP regulations. By signing this protocol, the investigator grants permission to Sumitomo Pharma Switzerland 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, hospital records 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. The CRO monitor will contact 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 GCPs. The study monitor should have access to any 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 an electronic database and combined with data provided from other sources in 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).

The intensity, frequency and scope of monitoring activities will be proportionate to the risks identified during the risk-assessment and ensure that study patient safety and rights are upheld, and data is of high quality. Centralized and remote monitoring is utilized in preference to site-based monitoring when appropriate and feasible.

Following the risk assessment, identified risks will be triaged and a study-specific monitoring plan will be developed. Standard centralized monitoring procedures for data quality will include programming of automatic error and plausibility checks within the ePRO sent to study patients. In addition, a variety of checks will be implemented within the central database. Monitoring will focus on patient safety and rights (conforming with regulatory requirements, informed consent) and source data verification.

Serious adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities and the World Health Organization Drug Dictionary Enhanced, respectively.

The CRO 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.

Records and documents pertaining to the conduct of this study must be retained by the CRO for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written

approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The CRO may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Site Monitoring Plan.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 2. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of Adverse Events

Adverse Events Definition

- An adverse event is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfil the definition of an adverse event or serious adverse event. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an adverse event or serious adverse event.
- **Selective safety data, including serious adverse events and nonserious adverse events leading to treatment discontinuation will be collected for this study.**

Events NOT Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness 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 disability/incapacity

- 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgement should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient

or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include 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.

Recording and Follow-Up of Adverse Events and Serious Adverse Events by the CRO

Adverse Event and Serious Adverse Event Recording

- Adverse events and serious adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative) using questionnaires. The CRO is responsible for checking the questionnaires for selective safety data (ie, serious adverse events and nonserious adverse events leading to treatment discontinuation) and for recording, reporting, and following up of these events. Serious adverse events and nonserious adverse events leading to discontinuation of relugolix or leuprolide acetate will also be reported directly by the principal investigator.
- The report will be assessed for seriousness and causal relationship to the study intervention by the CRO.
- Reports meeting the minimum criteria for reporting, that are assessed as serious, will be sent to the sponsor as a source record with all available information within 5 calendar days of CRO awareness of the information (unless there are unexpected fatal or life-threatening suspected adverse reaction reports in which case they will be reported to the sponsor or designee within 2 business/3 calendar days, whichever is shorter), with the Day 0 as the date the record is electronically received by the CRO. If new information about the case is gained in the process of case validation or follow-up, ie, after contacting the patient and/or physician, the follow-up source will be sent to the sponsor within 5 calendar days of receipt of the new information unless there are unexpected fatal or life-threatening suspected adverse reaction reports in which case they will be reported to the sponsor or designee within 2 business/3 calendar days, whichever is shorter.
- The CRO will record all relevant serious adverse event and nonserious adverse event leading to treatment discontinuation data in the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or their representative. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission.
- The CRO will attempt to confirm a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as a serious adverse event.
- All overdose events are to be reported within 5 calendar days of awareness by the CRO to the sponsor (or designee), whether or not the overdose is associated with an adverse event.

Assessment of Severity

For selective safety data not submitted directly by the investigator (with investigator assessment of severity), the CRO will make an assessment of severity for each serious adverse event and nonserious

adverse event leading to treatment discontinuation reported during the treatment period according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) using the available information. For diseases not specified with the CTCAE, the criteria below should be used to determine the grade severity:

Severity 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

Note: An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

For selective safety data not submitted directly by the investigator (with investigator assessment of causality), the CRO is obligated to assess the relationship between study intervention and each occurrence of each serious adverse event. The CRO drug safety physicians are responsible for assessing the causality.

A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The CRO will use clinical judgement to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The CRO drug safety physician will also consult the relugolix investigator brochure and/or Product Information, for marketed products, in his/her assessment.

For each serious adverse event reported, the CRO drug safety physician **must** document that he/she has reviewed the adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the CRO has minimal information to include in the initial report. However, it is very important that the CRO always makes an assessment of causality for every event before the initial transmission of the serious adverse event report. The CRO drug safety physician may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions are to be used for the relationship of the adverse event to study intervention:

- **Probably related**: 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 readministration (rechallenge) or withdrawal (dechallenge).
- **Possibly related**: 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.

Follow-up of Serious Adverse Events

- All serious adverse events will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3).
- If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology, if available.
- New or updated information will be recorded in the originally completed CRF.

The CRO will submit any updated serious adverse event data within 5 calendar days of electronic data capture. Unless there are unexpected fatal or life-threatening suspected adverse reaction reports, in which case they will be reported within 2 business/3 calendar days, whichever is shorter.

Reporting of Adverse Events and Serious Adverse Events by the Recruiting Physician

Adverse Event and Serious Adverse Event Reporting
• Adverse events and serious adverse events may also be reported by the patient (or caregiver, surrogate, or patient's legally authorized representative) directly to the recruiting physician. If the physician becomes aware of any serious adverse events or nonserious adverse events leading to treatment discontinuation, the recruiting physician is responsible for reporting these selective safety data to the sponsor (or designee). • E-mail transmission is the preferred method to transmit this information to the sponsor (or designee) for inclusion in the global safety database. • All overdose events are to be reported within 8 calendar days of awareness by the recruiting physician to the sponsor (or designee), whether or not the overdose is associated with an adverse event. The contact information for submission of serious adverse events, nonserious adverse events leading to treatment discontinuation, and events of overdose is provided on the study MVT-601-056 safety report form and in the safety management plan.
The initial report should include: • Study number (MVT-601-056) • Site address and number • Investigator name • Patient ID number, sex, and age • Details of study intervention administration • The date of the report • A description of the event (event term, seriousness of the event, date of onset, severity per CTCAE) • Causal relationship to the study intervention If the patient died, the report should include the cause of death as the event term (with death as outcome) and whether or not the event leading to death was related to study intervention treatment, 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 that are either unexpected and possibly related or expected serious adverse events that are assessed as potential risks (Section 2.3) and adjudicated MACE events (or those suspect MACE events pending adjudication) will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

APPENDIX 3. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of relugolix (ORGOVYX (relugolix) USPI 2023).

Male patients with partners who become pregnant

- The clinical research organization or investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive relugolix.
- The investigator is to report a female partner pregnancy to the CRO within 8 calendar days of awareness and the CRO is to report a female partner pregnancy to the sponsor within 5 calendar days of awareness.
- After the necessary signed release of information form from the pregnant female partner is obtained, the clinical research organization or investigator will record additional pregnancy information on the appropriate form and the CRO will submit it to the sponsor within 5 days of receipt of the information. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

APPENDIX 4. ELECTRONIC HEALTHCARE DATA SOURCES

Source data for this trial will be obtained from multiple electronic health record systems, depending on the site and where the patient may have received hospital care. Data will be reviewed by the clinical research organization to ensure completeness; if questions arise, further queries to the patient, patient's physicians, or source of the medical records (eg, hospital, emergency department) will be made as appropriate. Questionnaires will ascertain where a certain possible event occurred to ensure completeness of the medical records. If possible, insurance claims data will also be used to check for completeness of event reporting and obtainment of appropriate source documents.

APPENDIX 5. PROTOCOL AMENDMENT 1

CLINICAL STUDY PROTOCOL

Protocol Title:	Relugolix Versus Leuprolide in Patients with Prostate Cancer: A Randomized, Open-Label Study to Assess Major Adverse Cardiovascular Events (REPLACE-CV)
Protocol Number:	MVT-601-056
Compound:	Relugolix
Study Phase:	Phase 3
Short Title:	Randomized Study to Evaluate MACE in Patients with Prostate Cancer Treated with Relugolix or Leuprolide Acetate
Sponsor Name:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Agency Identifier Numbers:	IND: 118736
Original:	26 August 2022
Amendment 1:	16 May 2023

CONFIDENTIALITY STATEMENT

APPENDIX 6. ABBREVIATIONS

Abbreviation	Definition
ADT	androgen deprivation therapy
CI	confidence interval
USPI	United States prescribing information
GCP	Good Clinical Practice
CFR	Code of Federal Regulations
CRF	case report form
CRO	clinical research organization
ECG	electrocardiogram
eCRF	electronic case report form
ERF	eligibility review form
FDA	Food and Drug Administration
GnRH	gonadotropin-releasing hormone
HbA1c	hemoglobin a1c
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committees
IND	investigational new drug
IRB	Institutional Review Boards
MACE	major adverse cardiovascular event
P-gp	P-glycoprotein
PSA	prostate-specific antigen
QTc	QT (interval) corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
SoA	Schedule of Activities
SOC	Standard of Care

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