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RESEARCH**

APPLICATION NUMBER:

214621Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	NDA 214621
Priority or Standard	Priority
Submit Date(s)	April 20, 2020
Received Date(s)	April 20, 2020
PDUFA Goal Date	December 20, 2020
Division/Office	OND/CDER/OOD/DO1
Review Completion Date	
Established Name	Relugolix
(Proposed) Trade Name	(b) (4)
Pharmacologic Class	Gonadotropin-releasing hormone (GnRH) receptor antagonist
Code name	TAK-385
Applicant	Myovant Sciences, Inc.
Formulation(s)	oral tablet
Dosing Regimen	One time loading dose of 360 mg followed by 120 mg daily
Applicant Proposed Indication(s)/Population(s)	RELUGOLIX is a gonadotropin-releasing hormone (GnRH) antagonist indicated for the treatment of patients with advanced prostate cancer.
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	RELUGOLIX is a gonadotropin-releasing hormone (GnRH) antagonist indicated for the treatment of patients with advanced prostate cancer.

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Additional Reviewers of Application

OPQ	
Microbiology	
OPDP	
OSI	
OSE/DEPI	
OSE/DMEPA	
OSE/DRISK	
Other	

OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, elimination
ADT	androgen deprivation therapy
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC ₀₋₂₄	area under the concentration-time curve from time zero to 24 hours
AUC _{0-∞}	area under the concentration-time curve from time zero extrapolated to infinity
AUC _{0-τ}	area under the concentration-time curve from time 0 to end of dosing interval, τ
AUC _{ss}	area under the concentration-time curve at steady state
BCRP	breast cancer resistance protein
Caco-2	colorectal adenocarcinoma cells
CI	confidence interval
CL _{cr}	creatinine clearance
C _{max}	maximum observed concentration
CNS	central nervous system
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough,ss}	trough concentration at steady state
CYP	cytochrome P450
EBRT	external beam radiation therapy
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30
EORTC-QLQ-PR25	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire PR25

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EQ-5D-5L	EuroQol 5-Dimension 5-Level Scale
ER	estrogen receptor
F1	first generation
F2	second generation
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMR	geometric mean ratio
GnRH	gonadotropin-releasing hormone
HbA1c	hemoglobin A1c
hERG	human ether-à-go-go-related gene
HR	hazard ratio
IC ₅₀	half maximal inhibitory concentration
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
LH	luteinizing hormone
MACE	major adverse cardiovascular event
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NDA	New Drug Application
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
PD	pharmacodynamic

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P-gp	P-glycoprotein
PLD	phospholipidosis
PopPK	population pharmacokinetic
PopPK/PD	population pharmacokinetic/pharmacodynamic
PSA	prostate-specific antigen
QT/QTc	QT-interval/corrected QT-interval
QTc	QT-interval corrected for heart rate
SAP	statistical analysis plan
SD	standard deviation
SMQ	Standardised Medical Dictionary for Regulatory Activities query
t_{max}	time to maximum observed concentration
ULN	upper limit of normal
US	United States

1 Executive Summary

1.1. Product Information

Relugolix is an oral small molecule gonadotropin-releasing hormone (GnRH) antagonist. GnRH antagonists cause gonadotropin suppression by competitively blocking GnRH receptors in the anterior pituitary gland, which prevents endogenous GnRH from inducing LH and FSH release from pituitary cells. This subsequently suppresses production and secretion of testosterone from Leydig cells in the testes, which results in decreased systemic testosterone concentrations.

Androgens such as testosterone have been shown to stimulate prostate cancer growth. Castration via either orchiectomy or administration of GnRH agonists or antagonists is a primary therapy for advanced or metastatic prostate cancer. Currently, all approved formulations of GnRH agonists and antagonists are injectable, while relugolix is orally administered. Relugolix is not currently FDA approved for any indication.

The Applicant submitted a new drug application (NDA) to support the following proposed indication:

RELUGOLIX is a gonadotropin-releasing hormone (GnRH) antagonist indicated for the treatment of patients with advanced prostate cancer.

The recommended indication is unchanged from the Applicant's proposed indication statement. The recommended dose of relugolix is a single loading dose of 360 mg on the first day of treatment followed by 120 mg taken once daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for regular approval of this application for relugolix is based on efficacy and safety from the HERO study, a multinational, randomized, open-label, parallel-group study in patients with advanced androgen-sensitive prostate cancer who required at least 1 year of continuous androgen deprivation therapy (ADT).

A total of 943 patients with androgen-sensitive advanced prostate cancer who required one year of ADT were enrolled at 155 centers globally, including North and South America, Europe, Asia, and the Rest of the World. The study population included patients with PSA biochemical relapse following primary surgical treatment or radiotherapy with curative intent, newly diagnosed metastatic prostate cancer, or advanced localized disease for which immediate primary surgical treatment or radiotherapy was unlikely to be curative. Patients were randomized 2:1 to relugolix 120 mg daily (n=624) orally once daily following a single oral loading dose of 360 mg, or to 3-month leuprolide 22.5 mg depot subcutaneous injections (or 11.25 mg in Japan and Taiwan) for 48 weeks (n=310). Randomization was stratified by geographic region

(Europe, North and South America, or Asia and Rest of World), presence of metastatic disease (yes/no), and age (≤ 75 years old or > 75 years old).

The primary objective of the HERO study was to demonstrate the ability of relugolix to achieve and maintain suppression of serum testosterone to castrate levels (< 50 ng/dL) through 48 weeks of treatment in patients with advanced prostate cancer. HERO met its primary endpoint, demonstrating that 96.7% (95% CI 94.9, 97.9) of patients who received relugolix achieved and maintained sustained testosterone suppression below castrate levels (< 50 ng/dL) from Week 5 Day 1 (Day 29) to Week 49 Day 1 (Day 337) with the lower bound of the 95% CI exceeding 90%. Meeting this endpoint is consistent with FDA draft guidance on developing gonadotropin-releasing hormone analogues for patients with advanced prostate cancer.

Secondary endpoints included evaluation of non-inferiority of relugolix compared with leuprolide, cumulative probability of testosterone suppression to < 50 ng/dL prior to dosing on Week 1 Day 4 (Day 4), cumulative probability of testosterone suppression to < 50 ng/dL prior to dosing on Week 3 Day 1 (Day 15), proportion of patients with PSA response at Week 3 Day 1 (Day 15) followed with confirmation at Week 5 Day 1 (Day 29), cumulative probability of testosterone suppression to < 20 ng/dL prior to dosing on Week 3 Day 1 (Day 15), and mean FSH levels at Week 25 Day 1 (Day 169). The Applicant's claim of non-inferiority between relugolix and leuprolide and the subsequent superiority claim for relugolix over leuprolide were found to be unacceptable. The use of a non-inferiority test in the HERO study was discussed with the Applicant during the IND phase of development prior to the study start and it was noted that this test was not acceptable (b) (4)

In addition, different censoring rules have been used in historical studies and the current HERO study, and this can affect the outcome estimates. With these issues, the constancy assumption (i.e. the similarity of the new non-inferiority trial to the historical trials) may not be valid. Thus, the FDA considers these analyses exploratory.

Of the secondary endpoints, the review team agrees with labeling the proportion of patients who attained testosterone suppression to < 20 ng/dL, 95% for the relugolix arm by Day 29, given the potential clinical relevance of deeper testosterone suppression.

Relugolix has a relatively short half-life and duration of testosterone suppression compared to depot injections of GnRH analogs, which may either be a potential clinical benefit if rapid recovery of testosterone is desired or may impact efficacy in the setting of low adherence. A substudy was conducted in all patients who completed 48 weeks of relugolix and did not receive subsequent androgen deprivation therapy for at least 90 days after discontinuation of relugolix ($n=137$). Based on Kaplan-Meier analyses, 55% of patients achieved testosterone levels above the lower limit of the normal range (> 280 ng/dL) or baseline at 90 days after discontinuation of relugolix. The safety profile of relugolix was consistent with other GnRH analogs. The most common ($> 10\%$) adverse reactions and laboratory abnormalities ($> 15\%$) in the relugolix arm were hot flush,

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glucose increased, triglycerides increased, musculoskeletal pain, hemoglobin decreased, alanine aminotransferase (ALT) increased, fatigue, aspartate aminotransferase (AST) increased, constipation, and diarrhea. These were similar between arms and are consistent with the known adverse event profile of androgen deprivation therapy. The incidence of Grade 3-4 adverse events was 18% on the relugolix arm and 21% on the leuprolide arm. Discontinuation due to an adverse event was higher (3.5%) in the relugolix arm compared to the leuprolide arm, with no single etiology contributing to this imbalance. (b) (4)

Overall, the safety profile of relugolix is acceptable for this patient population with a serious and life-threatening disease.

In summary, the review team considers the benefit/risk profile of relugolix to be favorable for the treatment of adult patients with advanced prostate cancer and recommends regular approval for the above indication.

1.3. Benefit-Risk Assessment (BRA)

Androgen deprivation or castration, either surgically or medically, has been used for the palliative treatment of advanced prostate cancer since the 1940s. Currently, there are multiple GnRH agonists and one GnRH antagonist approved for the treatment of advanced prostate cancer via testosterone suppression. Relugolix is an oral GnRH antagonist that has not been previously approved by the FDA.

The safety and efficacy of relugolix were assessed in an open-label, randomized, multi-center, parallel-group study (HERO) in patients with prostate cancer. A total of 934 patients were randomized in a 2:1 ratio to receive either oral relugolix (360 mg loading dose on Day 1 followed by 120 mg daily) or leuprolide acetate subcutaneous injections every 3 months (22.5 mg, or 11.25 mg in Japan and Taiwan). Serum testosterone concentrations were measured at screening and on Days 1, 4, 8, 15, and 29 in the first month, then monthly through Week 48. Of the patients randomized, 32% had metastatic disease and 59% had either locally advanced or localized disease, and 10% were not classifiable. The major efficacy outcome was medical castration rate, defined as achieving and maintaining serum testosterone suppression to castrate levels (<50 ng/dL) by Day 29 through 48 weeks of treatment. The results demonstrated that the probabilities of medical castration were 96.7% (95% CI: 94.9%, 97.9%) for relugolix. The lower bound of the 95% interval exceeding 90%, consistent with FDA guidance on substantial evidence of efficacy for GnRH agents for achieving and maintaining castration. Additionally, 95% of patients treated with relugolix achieved a testosterone level < 20 ng/dL by Day 29, a deeper level of testosterone suppression which has potential clinical relevance. The review team did not consider the Applicant's claims of non-inferiority and superiority of relugolix compared to leuprolide acetate to be valid due to the unacceptability of the non-inferiority design. Secondary endpoints of FSH and LH reductions were consistent with the mechanism of relugolix and the changes in PSA were consistent with the hormone responsiveness of the diseases in the studied patients.

The safety analyses of HERO demonstrated that adverse reactions were generally comparable between relugolix and leuprolide and were consistent with other GnRH analogs. The most common (>10%) adverse reactions and laboratory abnormalities (>15%) in the relugolix arm were hot flush, glucose increased, triglycerides increased, musculoskeletal pain, hemoglobin decreased, alanine aminotransferase (ALT) increased, fatigue, aspartate aminotransferase (AST) increased, constipation, and diarrhea. Warnings common to other GnRH analogs, including QT/QTc prolongation, embryo-fetal toxicity, and pituitary-

gonadal axis suppression will be included in labeling. (b) (4)

Overall, the safety profile appears acceptable for the treatment of patients with advanced prostate cancer.

The review team considers the benefit/risk profile of relugolix acceptable for the treatment of advanced prostate cancer and recommends regular approval for this indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Prostate cancer is a serious and life-threatening condition. The 5-year survival rate for men with advanced or metastatic prostate cancer ranges from 26% to 30. There will be an estimated 33,000 deaths due to prostate cancer in 2020, which will comprise approximately 5% of all cancer related deaths. The relative 5-year survival for patients with localized disease is 76%, for regional disease spread to the lymph nodes 13%, for distant metastatic disease 6%, and for unstaged patients 5%. Patients with metastatic prostate cancer are also at risk for significant morbidity, including complications such as skeletal-related events. Cardiovascular disease is a competing cause of death and the most common non-cancer cause of death in this patient population.	Advanced prostate cancer is a serious and life-threatening condition that can result in significant morbidity and mortality if left untreated.
Current Treatment Options	Androgens such as testosterone have been shown to stimulate prostate cancer growth. Castration has been used to treat prostate cancer for decades with various methods, including surgical castration by orchiectomy or medical castration by GnRH agonists or GnRH antagonists. The most commonly used GnRH agonist is	There are currently available therapies that are used for the proposed indication. These options are injection drugs given as depots every several weeks or months. There is currently no oral daily option for testosterone

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>leuprolide. A GnRH antagonist that is FDA approved for patients with prostate cancer is degarelix, which was approved in 2008. Relugolix is not currently FDA approved for any indication.</p>	<p>suppression available in the U.S.</p>
<p>Benefit</p>	<p>The primary objective of the HERO study was to demonstrate the ability of relugolix to achieve and maintain suppression of serum testosterone to castrate levels (<50 ng/dL) through 48 weeks of treatment in patients with advanced prostate cancer. HERO met its primary endpoint, demonstrating that 96.7% (95% CI 94.9, 97.9) of patients who received relugolix achieved and maintained sustained testosterone suppression below castrate levels (<50 ng/dL) from Week 5 Day 1 (Day 29) to Week 49 Day 1 (Day 337) with the lower bound of the 95% CI exceeding 90%. Meeting this endpoint is consistent with FDA draft guidance on developing gonadotropin-releasing hormone analogues for patients with advanced prostate cancer. Secondary endpoints were supportive of the efficacy of relugolix.</p>	<p>Relugolix achieved and maintained sustained castration testosterone suppression below castrate levels with the lower bound of the 95% confidence interval exceeding 90%. These findings adequately demonstrate the efficacy of relugolix for the proposed indication.</p>
<p>Risk and Risk Management</p>	<p>The adverse event profile of relugolix was similar to those for other GnRH analogs, was comparable between the relugolix and leuprolide arms of HERO, and included hot flush, musculoskeletal pain, and fatigue as well as glucose and triglyceride increases as the most common adverse reactions and laboratory abnormalities.</p> <p>Serious adverse reactions occurred in 12% of patients receiving relugolix on HERO and included myocardial infarction, acute kidney injury, arrhythmia, hemorrhage, and urinary tract infection.</p>	<p>The safety profile is acceptable for the intended population. Labeled warnings will include QT/QTc prolongation, embryo-fetal toxicity, and pituitary gonadal system suppression, which are common to other GnRH analogs.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input type="checkbox"/>	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
<input type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input type="checkbox"/>	<input type="checkbox"/> Patient-reported outcome (PRO)	Section 8.1.1
<input type="checkbox"/>	<input type="checkbox"/> Observer reported outcome (ObsRO)	N/A
<input type="checkbox"/>	<input type="checkbox"/> Clinician reported outcome (ClinRO)	N/A
<input type="checkbox"/>	<input type="checkbox"/> Performance outcome (PerfO)	N/A
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	N/A
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	Section 8.1.1
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	N/A
<input type="checkbox"/>	Natural history studies	N/A
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	N/A
<input type="checkbox"/>	Other: (Please specify)	N/A
	Patient experience data that was not submitted in the application, but was considered in this review.	Additional information was submitted by means of a response to FDA information request and has been considered in the review of this application.

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Prostate cancer is the second most common cancer in men worldwide, with over 1.2 million cases and 358,000 deaths annually (Bray et al. 2018). It is projected that approximately 11.6% of men in the United States (US) will be diagnosed with prostate cancer at some point during their lifetime (NIH 2019). Men with disease progression including biochemical (prostate-specific antigen [PSA]) relapse following primary surgical treatment or radiotherapy with curative intent, advanced localized disease for which immediate primary surgical treatment or radiotherapy was unlikely to be curative, and men with metastatic disease are said to have advanced prostate cancer. Prostate cancer cells are highly dependent upon androgens, including testosterone and dihydrotestosterone, for growth. Thus, antigen deprivation therapy (ADT) or medical castration has been and remains the foundational therapy for the treatment of patients with advanced prostate cancer (Parker et al. 2015; Attard et al. 2016). When there is progression of the disease despite castrate levels of testosterone, ADT remains the backbone of treatment to which other treatment options are added (Mohler and Antonarakis 2019). Therefore, in patients with advanced prostate cancer, treatment is usually continued upon development of nonmetastatic and metastatic castration-resistant prostate cancer (Mohler and Antonarakis 2019).

Prostate cancer is a relatively slow-growing malignancy, and men may remain asymptomatic for years, but the 5-year survival rate for men with advanced or metastatic prostate cancer ranges from 26% to 30% (Steele et al. 2017; Ritch and Cookson 2018). Patients with metastatic prostate cancer have a high risk of life-threatening complications that increases with time, including skeletal-related events such as spinal cord compression, vertebral collapse, and pathological fractures (Auclerc et al. 2000; McMurtry and McMurtry 2003). They are often plagued with fatigue, frailty, and bone pain, limiting their quality of life. With the advent of better treatments, however, more men with prostate cancer are living longer and, in this population, cardiovascular disease is the most common non-cancer cause of death. Deaths from cardiovascular disease now exceed those from prostate cancer in men with prostate cancer (Satariano et al. 1998; Bhatia et al. 2016).

The FDA's Assessment:

The FDA agrees with the Applicant's position that prostate cancer is a common malignancy, ADT is a foundational therapy for patients with advanced prostate cancer, and patients with metastatic disease have a high risk of life-threatening complications from this disease. Advanced prostate cancer is a serious medical condition associated with significant morbidity and mortality. Treatment strategies for advanced and

metastatic prostate cancer have typically focused on testosterone suppression, and ADT has been used for this purpose for several decades.

2.2. Analysis of Current Treatment Options

Gonadotropin-releasing hormone (GnRH) receptor agonists result in desensitization and down regulation of the hypothalamic-pituitary-gonadal axis (Mcleod 2003; Sharifi et al. 2005) and are the current mainstay of medical androgen deprivation. As agonists of the GnRH receptor, drugs such as leuprolide [Lupron Depot® and Eligard®] and goserelin acetate (Zoladex®) initially stimulate the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH); however, the continuous stimulation leads to desensitization and subsequent suppression of LH and to a lesser extent FSH release (Labrie et al. 2005). Initial administration of GnRH agonists results in a testosterone surge and in some patients, a clinical flare with an increase in clinical symptoms such as bone pain, spinal cord compression, pathologic fracture, and bladder outlet obstruction (Oh et al. 2010; Eligard Prescribing Information 2019; Lupron Prescribing Information 2019) in up to 63% of patients (Mahler 1993; Bublely 2001). The initial clinical flare is often managed with simultaneous administration of an antiandrogen (Thompson 2001) such as bicalutamide. Use of bicalutamide has been associated with hepatotoxicity requiring monitoring of transaminases and gynecomastia (Casodex USPI 2017).

Men with prostate cancer are at higher risk of developing cardiovascular disease, and this risk increases with the use of GnRH receptor agonists (Keating et al. 2010a). Risk of cardiovascular disease with GnRH receptor agonists is higher than that observed with GnRH receptor antagonists, particularly in men with pre-existing cardiovascular disease (Saigal et al. 2007; Keating et al. 2010a; Margel et al. 2019). Lupron Depot and Eligard labels include a warning of an increased risk of myocardial infarction, sudden cardiac death, and stroke associated with use of GnRH receptor analogues in men and recommend that patients be monitored for symptoms and signs suggestive of development of cardiovascular disease (Eligard Prescribing Information 2019; Lupron Prescribing Information 2019).

The only GnRH receptor antagonist currently available for the treatment of prostate cancer in the US, degarelix (Firmagon®), is not associated with an initial testosterone surge and clinical flare. However, use of degarelix in the clinical setting is limited due to a high injection volume, frequent injection site reactions, and the need for monthly injections, which makes the injection site reactions less tolerable. Gonadotropin-releasing hormone receptor agonists, therefore, remain the current standard of care.

Current ADT options, including GnRH agonists and degarelix, are only available in injectable depot formulations and their effects on testosterone suppression to castrate levels may persist for months following discontinuation of therapy, prolonging the safety concerns and symptoms associated with therapy (Nascimento et al. 2019). The probability and time to return of serum testosterone to greater than castrate

concentrations are highly variable and can depend on a number of factors, including ADT duration and the patient's age (Bong et al. 2008). Studies have shown that longer ADT duration is associated with delayed and lower recovery rates (Kaku et al. 2006; Murthy et al. 2006). Persistently low testosterone concentrations are associated with a wide variety of adverse events, including carbohydrate and lipid metabolic abnormalities, bone mineral density loss, cardiovascular events, and cognitive dysfunction (Nguyen et al. 2015). In addition, ADT is also known to cause sexual dysfunction; patients report reduced sex drive and erectile dysfunction secondary to alterations of the corpus cavernosum smooth muscle (Aversa et al. 2019). An additional disadvantage of this protracted or even failed return of testosterone concentrations above castrate levels with injectable depot formulations is the inability to stop the treatment effect rapidly in serious medical situations in which the anabolic effect of testosterone may be desirable to enhance recovery (eg, myocardial infarction, hip fracture, stroke).

An overview of GnRH receptor antagonists and receptor agonists approved by the US Food and Drug Administration (FDA) is provided in [Table 1](#).

Table 1: Available FDA-Approved Therapies for the Proposed Indication

Product Name	Relevant Indication	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
GnRH Receptor Agonists				
Leuprolide (Lupron Depot®, approved in 1989)	Palliative treatment of advanced prostatic cancer	Lupron Depot 7.5 mg (Q1M), 22.5 mg (Q3M), 30 mg (Q4M), or 45 mg (Q6M), administered by IM injection	<p><u>Primary Endpoint:</u> Percent of patients at castrate level (testosterone < 50 ng/dL) by 30 days and maintained through 24 weeks of treatment: 22.5 mg (Q3M): 95% (87/92) For other depot formulations the results were: 7.5 mg (Q1M) for 24 weeks: 94% (51/54), 30 mg (Q4M) for 32 weeks: 94% (46/49), 45 mg (Q6M) for 48 weeks: 93% (138/148) from Weeks 4-48.</p> <p><u>Secondary Endpoints:</u> Objective tumor response: 22.5 mg (Q3M): No progression in 85% (78/92) of patients during the initial 24 weeks of treatment, 7.5 mg (Q1M): No progression in 77% (40/52) of patients at Week 12, 84% (42/50) at Week 24, 30 mg (Q4M): No progression in 86% (37/43) of patients at Week 16, 77% (37/48) at Week 32.</p>	Increased serum testosterone (flare), hyperglycemia and diabetes, cardiovascular diseases, effect on QT/QTc interval, convulsions, increased risk of myocardial infarction, sudden cardiac death, and stroke.

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Leuprolide (Eligard® approved in 2002)	Palliative treatment of advanced prostatic cancer	Eligard 7.5 mg (Q1M), 22.5 mg(Q3M), 30 mg (Q4M), or 45 mg (Q6M), administered by SC injection	<p><u>Primary Endpoint:</u> Percent of patients at castrate level (testosterone < 50 ng/dL) by 28 days and maintained through 6 months: 22.5 mg (Q3M): 99% (115/116). For other depot formulations the results were: 7.5 mg (Q1M) for 6 months: 94% (112/119), 30 mg (Q4M) for 8 months: 96% (85/89), 45 mg (Q6M) for 12 months: 99% (108/109).</p> <p><u>Secondary Endpoints:</u> Decrease in PSA levels at conclusion of studies: 22.5 mg (Q3M): 98% reduction, 7.5 mg (Q1M): 94% reduction, 30 mg (Q4M): 86% reduction, 45 mg (Q6M): 97% reduction.</p>	Increased serum testosterone (flare), hyperglycemia and diabetes, cardiovascular diseases, effect on QT/QTc interval, convulsions, increased risk of myocardial infarction, sudden cardiac death, and stroke.
GnRH Receptor Antagonists				
Degarelix (Firmagon®, approved in 2008)	Treatment of patients with advanced prostate cancer	Degarelix 240 mg (given as two SC injections of 120 mg each), followed by maintenance doses of 80 mg every 28 days by SC injection	<p><u>Primary Endpoint:</u> 97.2% (202/207) of patients achieved castrate level (testosterone ≤ 50 ng/dL) by 28 days and maintained it through 12 months of treatment.</p> <p><u>Secondary Endpoint:</u> Serum PSA levels were lowered by 64% after 2 weeks, 85% after 1 month, 95% after 3 months, and remain suppressed throughout 12 months of treatment with degarelix.</p>	Long-term ADT prolongs the QT interval, hypersensitivity reactions, injection site reactions (eg, pain, erythema, swelling or induration).

Abbreviations: ADT = androgen deprivation therapy; IM = intramuscular; PSA = prostate-specific antigen; Q1M = monthly; Q3M = every 3 months; Q4M = every 4 months; Q6M = every 6 months; SC = subcutaneous.

Sources: Eligard Prescribing Information 2019; Lupron Prescribing Information 2019; Firmagon Prescribing Information 2020.

The Applicant's Position:

Prostate cancer is a serious condition with increasing morbidity and mortality across the disease continuum of advanced prostate cancer. Androgens promote the growth of prostate cancer and ADT is the foundational treatment for advanced prostate cancer (Parker et al. 2015; Attard et al. 2016). Despite available therapies, men with prostate cancer could benefit from an oral treatment that lowers testosterone within days without a testosterone surge and the potential for clinical flare, and more predictably recovers testosterone levels upon discontinuation of treatment. An ADT that does not increase the early risk of major adverse cardiovascular events reported in men taking GnRH agonists, particularly for the large population of men with preexisting cardiovascular disease or with risk factors for cardiovascular disease, would be of benefit. Furthermore, an oral formulation could eliminate the risk of injection site reactions and would not require regular in-person clinic visits for injections, a potential benefit for some men with advanced prostate cancer.

GnRH receptor agonists, available only in injectable 1 – 6 monthly depot formulations, result in a testosterone surge and risk of clinical flare particularly for men with metastatic disease and their effects on testosterone suppression to castrate levels may persist for months following discontinuation of therapy. Prolonged testosterone suppression can increase the safety risks and symptoms associated with ADT. Degarelix, an approved GnRH receptor antagonist, is only available as a monthly depot injection and is associated with a high frequency of injection site reactions that limit its use in the clinic and a slow recovery of testosterone after discontinuation of treatment.

Relugolix represents a potential therapeutic option with a more favorable benefit:risk profile without the disadvantages of the current standard of care for ADT in men with advanced prostate cancer. Once daily relugolix achieves testosterone suppression within days without a testosterone surge and potential clinical flare, provides sustained testosterone suppression (b) (4) and allows more control over treatment duration with testosterone concentrations recovering to normal levels on average within 90 days.

The FDA's Assessment:

The FDA agrees that prostate cancer is a serious condition and the currently available treatment options outlined by the Applicant appear to be accurate.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Relugolix is not currently marketed in the US. Relugolix monotherapy (40 mg) has been commercialized in Japan since 2019 for treatment of symptoms associated with uterine fibroids under the brand name Relumina®.

[Redacted]

(b) (4)

The FDA's Assessment:

The FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Myovant has developed relugolix 120-mg tablets as monotherapy for the treatment of patients with advanced prostate cancer.

Original sponsorship of IND 118,736 (for the treatment of advanced prostate cancer) was transferred from Takeda to Myovant on 03 May 2016 for continued development.

Key input from FDA on elements of the development program for relugolix in prostate cancer is described below.

In October 2015, the former sponsor of IND 118,736 (Millennium Pharmaceuticals, Inc. [Millennium] a subsidiary of Takeda) obtained advice from the FDA in an end-of-phase 2 meeting to gain agreement on the phase 3 program for relugolix to support an indication for the treatment of patients with advanced prostate cancer. Agreement was reached on the overall design of the phase 3 study, including the definition of the primary endpoint as the sustained castration rate from Week 5 Day 1 (Day 29) through Week 49 Day 1 (Day 337), and the use of the Kaplan-Meier method to analyze the primary endpoint. Aspects of the statistical analysis plan (SAP), including censoring rules, were also discussed.

[Redacted]

(b) (4)

In July 2019, a Type C meeting was held with the FDA to discuss and agree to the original SAP for the pivotal study MVT-601-3201. Myovant incorporated feedback from the FDA including the additions for sensitivity analyses and an analysis using the Ischemic Heart Disease Standardised MedDRA query (SMQ) that includes all ischemic cardiovascular disease in addition to myocardial infarction. The updated SAP was based on protocol

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Amendment 3 and included modifications to the censoring rules and testing procedures for the primary and alpha-protected secondary endpoints.

The FDA accepted the agreed initial pediatric study plan (14 Jan 2019), and Myovant requested a full waiver of pediatric studies in males and females < 17 years of age.

During a Type C meeting (06 Aug 2019), the FDA agreed that the proposed clinical pharmacology program would support a marketing application, and the human absorption, distribution, metabolism, elimination (ADME) study performed with an 80-mg dose of relugolix would support the characterization of the ADME profile of the to-be-marketed 120-mg dose. Furthermore, upon review of the study designs, the FDA agreed that six dedicated drug interaction studies (in planning or execution) would support the assessment of the potential effect of relugolix as a victim and perpetrator of drug interactions.

During a Pre-New Drug Application (NDA) meeting with the FDA (04 Feb 2020) the FDA agreed with the nonclinical and clinical content and the format and structure of the NDA, including integrated analysis plans and datasets to support analysis of major adverse cardiac events (MACE). The Agency agreed with Myovant's plan to provide an integrated analysis of efficacy and not to pool studies. In regard to safety, FDA stated that the focus of the primary analysis should be the pivotal study MVT-601-3201 but agreed to pooling this data with the dose-finding study C27002 which was also conducted in advanced prostate cancer, and the proposed integrated analysis of safety. The FDA stated priority review would be determined at the time of NDA submission based on providing further justification of a potential advantage in improvement of benefit:risk relative to all available treatment options, including leuprolide and degarelix. Additionally, the FDA suggested consideration for the use of the Assessment Aid to facilitate the NDA review.

(b) (4)

NDA 214, 621 was submitted 20 Apr 2020.

The FDA's Assessment:

In October of 2015, the FDA communicated to the Applicant that it did not agree with the proposed non-inferiority test (b) (4)

a non-inferiority test would not be appropriate.

The FDA also did not agree with the Applicant's proposed analysis methods for the

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secondary endpoints, stating that descriptive analyses should be performed for both arms.

In July of 2019, the FDA communicated to the Applicant that the primary analysis for HERO should be the single-arm confidence interval approach, and that additional analyses as outlined by the Applicant would be considered exploratory.

The FDA agrees with the other aspects of the Applicant's position.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

The Office of Scientific Investigations (OSI) identified GCP deficiencies at Study Site 2004 for study HERO, which included underreporting of adverse events for several subjects who received study treatment in combination with other therapies, including chemotherapy and/or radiotherapy outside the study side. The Applicant re-evaluated this site and confirmed seven unreported adverse events identified by the FDA as well as 22 events through re-verification of the source data. None of these events were Grade 3 or above or serious events. The FDA does not consider that these unreported events meaningfully impacts the assessment of the overall safety profile of relugolix. Based on a root cause analysis, the Applicant considers, and the FDA agrees, that the deficiencies appeared specific to the site in question.

4.2. Product Quality

The product quality review team recommends approval of this NDA based on adequate CMC information submitted in the NDA and an acceptable recommendation from the facilities review.

The review team requested, and the Applicant agreed to, PMC #3962-1: "Submit test report for the currently ongoing study titled "The Zebrafish Extended One-Generation Reproduction Test" to support of the environmental risk assessment for relugolix." The final report date is August 31, 2021.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA's Assessment

Relugolix is an orally available, non-peptide small molecule with an established pharmacological class of gonadotropin-releasing hormone (GnRH) receptor antagonist and is proposed for the treatment of patients with advanced prostate cancer. The nonclinical development program for relugolix consisted of studies in mice, rats, monkeys and rabbits to evaluate primary pharmacology, safety pharmacology, general toxicology, reproductive and developmental toxicology, carcinogenicity and genotoxic and phototoxic potential. While some of these studies were not necessary based on the advanced cancer indication as per ICH S9 (b) (4)

In vitro, relugolix exhibited similar binding affinities to human and monkey GnRH receptors with IC₅₀ values of 0.12 and 0.15 nM, respectively. In contrast, a 19,000x and 24,000x reduction in binding affinity was noted to rat GnRH receptor (IC₅₀ = 2900 nM) compared to monkey and human receptors, respectively. Relugolix showed antagonist activity by inhibiting arachidonic acid release from GnRH-induced CHO cells expressing human or monkey GnRH receptors. In vivo, administration of relugolix suppressed the pituitary-gonadal axis, causing a decrease in plasma luteinizing hormone in castrated monkeys after a single dose and reduction of serum testosterone levels in human GnRH receptor knock-in male mice after repeat dosing. Male knock-in mice receiving relugolix twice a day for 28 days had a reduction in prostate, seminal vesicles and testis organ weights comparable to castrate levels. The effects on ventral prostate weight but not testis recovered after discontinuation of relugolix, while relugolix-induced suppression of serum testosterone levels showed variable reversibility 28 days after discontinuation. Reduction of luteinizing hormone, follicle stimulating hormone and testosterone levels were also noted clinically after oral administration of the recommended loading dose of 360 mg, followed by 120 mg per day.

In secondary pharmacology studies, 10 µM relugolix inhibited human tachykinin NK₂ receptors by 55%. The approximate IC₅₀ (6.24 µg/mL) for the tachykinin NK₂ receptors is 134 times the C_{max} in humans at the recommended dosing regimen. In safety pharmacology studies, there were no relugolix-related adverse effects on the central nervous and respiratory systems in rats at doses up to 2000 mg/kg. While relugolix was a low-potency hERG blocker in vitro (IC₅₀ = 9.7 µg/mL), a single dose of relugolix in monkeys resulted in QT/QTc prolongation of up to 47 msec at ≥ 100 mg/kg (90 times the human C_{max} based on toxicokinetics from a 4-week repeat-dose monkey study). In the clinic, prolongation of QTc interval (> 10 msec) was not reported after single doses of relugolix at 60 mg and 360 mg. In general, androgen deprivation therapy may prolong QT/QTc interval.

Relugolix

Relugolix exposure was 21x less (based on AUC) in monkeys administered an oral dose under fed compared to fasted conditions. Following a single oral administration of relugolix to fasted animals, T_{max} occurred at ~3 h in rats and 0.8 to 1.8 h in monkeys. Toxicokinetics from repeat-dose studies in rats (26-weeks) and monkeys (39-weeks) showed relugolix exposure was greater than dose proportional at dose ranges evaluated. Following a single oral dose of radiolabeled relugolix to rats, the highest radioactivity was observed in liver, intestine, thyroid, stomach and pituitary gland. Radioactivity in the eyes, mainly localized to the melanin rich tissues - anterior and posterior parts, was detected at 4 h and sustained for up to 12 weeks post-dose. Fecal elimination was the major route of excretion of total radioactivity in both rats (>96%) and monkeys (>90%). The *N*-demethoxylated metabolite of relugolix, Metabolite-C, was excreted in feces, representing 59% and 45% of the dose administered in rats and monkeys, respectively.

Despite the marked low-affinity binding to rat GnRH receptors, the Applicant used rats to evaluate general and reproductive toxicology and carcinogenicity. These studies can inform on off-target effects of relugolix and its metabolites or impurities but are most likely not biologically relevant to characterize direct effects of GnRH receptor inhibition on reproductive and developmental toxicology and perhaps carcinogenicity.

The repeat-dose toxicity studies for relugolix were conducted in mice (up to 13 weeks), rats (up to 26-weeks) and monkeys (up to 39 weeks) using the intended oral route of administration. Of note, only the 39-week monkey study included a recovery phase. Monkeys were the most sensitive species and possibly reflect the most toxicologically relevant species based on binding affinity. Relugolix caused liver toxicity (increased liver enzymes with or without histopathology correlates of up to severe yellow/brown pigment deposition and up to moderate bile plug) in monkeys at ≥ 50 mg/kg/day (approximately 53x the clinical exposure based on AUC). This effect exhibited some reversibility. Increased liver enzymes were also reported in rats at 2000 mg/kg/day in the 4-week study. Increased ALT and AST levels were reported among the most common adverse reactions in patients with advanced prostate cancer receiving relugolix at the recommended dosing regimen.

In repeat-dose studies, phospholipidosis in multiple organs was observed in both rats (≥ 100 mg/kg) and monkeys (≥ 1.5 mg/kg) at exposures 18 times and 0.6 times, respectively, the clinical exposure at the human recommended dose based on AUC. In general, phospholipidosis did not compromise organ function, except at doses that caused high exposure and mortality in rats (at ≥ 1000 mg/kg/day, approximately 251x the clinical exposure based on AUC). Reversibility was noted in the monkey study. The significance of this finding is unknown to humans and was not observed in clinical studies at daily doses up to 120 mg for up to 24-weeks. Animal findings of phospholipidosis were included in the label in Section 13.2 Animal Toxicology and/or Pharmacology.

In rodents, nephrotoxicity was noted in mice (decreased weight, with minimal renal tubular epithelium necrosis and increased renal tubular basophilia) in the 13-week study at 2000 mg/kg/day (approximately 929x the clinical exposure based on AUC); and in rats in the 4-week study at 2000 mg/kg/day and in the 2-year carcinogenicity study at 600 mg/kg/day (approximately 462x and 225x, respectively, the clinical exposure based on AUC). Kidney histopathological changes in rats included up to moderate tubular cell vacuolation, regeneration and dilatation of the renal tubules, hyaline casts, hyaline droplets, inflammatory cell infiltration and/or hyperplasia in the papilla. Acute kidney injury was reported as a serious adverse reaction occurring in 0.6% of patients receiving relugolix.

Reproductive and developmental toxicology studies were conducted in rats and rabbits. In a fertility and early embryonic development study in rats, oral administration of relugolix at doses up to 1000 mg/kg/day had no adverse effects on fertility, mating or early embryonic development. In the 39-week study in monkeys, relugolix did not induce toxicities in male reproductive organs but caused reversible cessation of menses in females starting on Day 13 of treatment. Based on the mechanism of action of GnRH receptor antagonists and consistent with primary pharmacology results using human GnRH receptors in male knock-in mice, relugolix is expected to impair fertility.

In an embryo-fetal development study in rabbits, oral administration of relugolix during the period of organogenesis resulted in embryo-fetal lethality at the highest dose tested, 9 mg/kg/day (approximately 0.3 times the human exposure at the recommended dose of 120 mg daily based on AUC). In the rat, oral administration of relugolix at doses up to 1000 mg/kg/day during the period of organogenesis resulted in reduced body weight (-4%) and body weight gain (up to -21%) and decreased food consumption (up to -29%) in dams at the high dose; however, these effects were low in magnitude and/or transient. There were no adverse effects on pregnancy or embryo-fetal parameters observed. In an ADME study, placental-feto transfer was confirmed following administration of radiolabeled relugolix to fasted pregnant rats (pregnancy day 18). The limited results noted in rats in reproductive and developmental parameters may be misleading given the low binding affinity of relugolix to rat receptors and thus, these results were not included in the label.

Based on abortion, total litter loss or decreased number of live fetuses in an embryo-fetal development study in rabbits and mechanism of action, the label includes a warning for embryo-fetal toxicity. The label also advises males with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of relugolix based on recommendations for duration of contraception for nongenotoxic pharmaceuticals that are embryo-fetal toxic from the FDA guidance, "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations." In an ADME study, relugolix and/or its metabolites were present in milk of lactating rats at concentrations 10-fold higher than in plasma after a single oral administration of radiolabeled relugolix. These findings were included in the label.

Relugolix

Relugolix was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay nor clastogenic in the in vitro chromosomal aberration assay and in vivo rat bone marrow micronucleus assay. However, an impurity and degradant of relugolix, (b) (4) was mutagenic in the Ames assay for TA98 S. typhimurium with rat S9 and showed mutagenic potential in the in silico evaluations based on its (b) (4) moiety structural alert. As a follow-up to this positive finding, (b) (4) was tested in additional in vitro genotoxicity studies in mammalian cells and in vivo studies. Results showed (b) (4) was not mutagenic nor clastogenic in the follow-up assessments. Furthermore, relugolix (containing (b) (4) times the clinical exposure based on the loading dose of 360 mg) administered to mice and rats at dose up to 100 mg/kg/day and 600 mg/kg/day, respectively for 2 years was not carcinogenic. Of note, dedicated carcinogenicity studies were not needed to support this NDA based on the advanced cancer indication. Based on the totality of data, relugolix and impurity (b) (4) are not considered to represent a genotoxic risk for the proposed indication.

To calculate animal to human exposure margins, the Applicant used PK parameters (C_{max} = 79.1 ng/mL and AUC = 556 ng.h/mL) derived from a drug interaction study in healthy subjects at a fixed dose of 120 mg per day. The FDA clinical pharmacology team recommended using human exposure data from 7 Japanese subjects in the pivotal phase 3 trial, who had intensive PK sampling. Additionally, these patients received the recommended administration of a loading dose of 360 mg on Day 1, followed by 120 mg per day. Therefore, exposure multiples were calculated using systemic geometric mean exposures of C_{max} and AUC values at steady-state of 46.4 ng/mL and 373 ng.h/mL, respectively.

Recommendation

Overall, the nonclinical data submitted to this NDA are adequate to support approval of (b) (4) for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for relugolix.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

5.3. Pharmacology

5.3.1. Primary Pharmacology

The FDA's Assessment:

Original studies plus a peer reviewed literature reference (Nakata et al 2014, European Journal Pharmacology 723: 167-174) were submitted to support the mechanism of action of relugolix (TAK-385). Key studies are summarized below:

Binding Affinity

To evaluate binding, TAK-385, TAK-013 (an analog of TAK-385), TAP-144 (leuprolide acetate; a GnRH agonist), cetrorelix (GnRH antagonist) or GnRH were incubated in the presence of ¹²⁵I-TAP-144 and human, monkey or rat GnRH receptors expressed in CHO cell membranes. Radioactivity was measured to determine inhibition of radiolabeled ligand binding to GnRH receptor-expressing cell membranes. In vitro, in the absence of serum (fetal bovine serum; FBS), TAK-385 bound to human, monkey and rat GnRH receptors with IC₅₀ values of 0.12, 0.15 and 2900 nM, respectively (Study# TAK-385-00090). Binding affinities decreased by 3-fold in the presence of 40% FBS for all GnRH receptors; nevertheless, TAK-385 bound to the human GnRH receptor with an IC₅₀ value of 0.33 nM, which was 3.6x and 9x higher when compared to IC₅₀ values of 1.2 nM and 3.0 nM for cetrorelix and leuprolide acetate (TAP-144), respectively, in the presence of 40% FBS. TAK-385 bound to human GnRH receptor with binding affinities ≥51x compared to GnRH with or without FBS.

Functional activity

In vitro: Cell based assays using CHO cells expressing human or monkey GnRH receptors evaluated the antagonist functionality of TAK-385 by monitoring GnRH induced arachidonic acid release. TAK-385 showed antagonist activity by inhibiting arachidonic acid release from GnRH-induced CHO cells expressing human GnRH receptors with IC₅₀ values of 0.32 nM in the absence of human plasma and 1.6 nM in the presence of 40% human plasma (Study# TAK-385-00091). In comparison, cetrorelix and TAK-013 (an analog of TAK-385) inhibited arachidonic acid release with IC₅₀ values of 0.67 nM and 0.068 nM in the absence of human plasma and 4.5 nM and 3.4 nM in the presence of 40% human plasma, respectively. Similarly, using a CHO cell system expressing monkey GnRH receptors, TAK-385 inhibited GnRH-induced arachidonic acid release with an IC₅₀ of 16 nM (Study# TAK-385-00092). This effect was reduced in the presence of 40% monkey plasma (IC₅₀ = 230 nM). In comparison, cetrorelix had IC₅₀ values of 0.78 nM and 12 nM in the absence or presence of 40% monkey plasma, respectively.

In vivo: The effects of TAK-385 on the pituitary-gonadal axis were evaluated by monitoring luteinizing hormone (LH) levels in castrated monkeys (Study# TAK-385-00095). A single oral administration of TAK-385 to castrated monkeys decreased plasma LH levels at doses of 1 and 3 mg/kg but not at lower doses (0.1 and 0.3 mg/kg).

Suppression of plasma LH levels were maintained for up to 24 h at 1 mg/kg and for 48 h at 3 mg/kg. Of note, 48 h was the last time point plasma was collected.

Given the low binding of relugolix to rat GnRH receptors, the effects of TAK-385 on weight of reproductive organs and mRNA expression of human GnRH receptor from isolated pituitaries were evaluated in male human GnRH receptor knock-in mice (Study# TAK-385-00105). Males (n=8/group) received 0 (5% methylcellulose), 3, 10 or 30 mg/kg TAK-385 orally, twice daily for 28 days, followed by collection of specific organs. For comparison, castrated male mice were used as a positive control. TAK-385 caused a statistically significant decrease in ventral prostate weight (up to -84% relative to body weight) and seminal vesicle weight (up to -91% relative to body weight) at ≥ 3 mg/kg, twice daily, demonstrating similar effects as castrated mice at ≥ 10 mg/kg, twice daily. Attenuation of pituitary human GnRH mRNA expression (up to -80%; $p \leq 0.05$), comparable to castrated mice, was noted at ≥ 10 mg/kg, twice daily. A selection of these results was also included in the publication (Nakata et al 2014, European Journal Pharmacology 723: 167-174) submitted to support primary pharmacology.

Nakata et al. included further results evaluating gonadal function recovery and effects of TAK-385 on female human GnRH knock-in mice; however, based on the proposed indication the review of this article focused on effects of TAK-385 on male mice. To investigate gonadal function recovery, male human GnRH knock-in mice (n=5/group) were treated with TAK-385 twice daily at 0 or 30 mg/kg for 28 days. An additional control group was orchietomized. At end of treatment, one male/group was euthanized to confirm effects of TAK-385; while the remaining animals were sacrificed 3, 7, 10, 14 or 28 days after last day of treatments to evaluate recovery of organ weights (testes and ventral prostate) and serum testosterone levels. Administration of TAK-385 significantly reduced testis weight at 10 mg/kg, twice daily and ventral prostate weight at ≥ 3 mg/kg, twice daily, with similar to castrate levels at 10 mg/kg, twice daily. The effects on ventral prostate weight but not testis recovered 28 days after discontinuation of TAK-385. TAK-385-induced suppression of serum testosterone levels showed reversibility after discontinuation; however, graphed results showed variability.

5.3.2. Secondary Pharmacology

The Applicant's Position:

Results of an in vitro study evaluating off-target effects in a series of 134 enzyme and radio-ligand binding assays suggest there is a low risk for off-target pharmacological effects with relugolix (TAK-385/00054). Relugolix caused > 50% inhibition (55%) of only the tachykinin NK₂ receptors at 10 μ M (6.24 μ g/mL). Based on IC₅₀ value of approximately 10 μ M, the inhibitory concentration of relugolix for the tachykinin NK₂ receptor is approximately 83,000-fold higher than that reported for the GnRH receptor (IC₅₀ 0.12 nM). Further, the approximate IC₅₀ for the tachykinin NK₂ receptor (~ 10 μ M) is ~ 79 -fold higher than the mean maximum observed concentration (C_{max}) of relugolix at steady state after administration of 120-mg doses, once daily (79.1 ng/mL). Relugolix

Relugolix

did not inhibit binding of ligands to the androgen receptor, estrogen receptors (ER α and ER β) or progesterone receptor. There was no significant binding to any of the remaining 133 targets. These data suggest there is a low risk for off-target pharmacological effects with relugolix.

The FDA's Assessment:

FDA agrees with the Applicant's conclusions. Based on the recommended PK parameters provided by the FDA's clinical pharmacology team, the approximate IC₅₀ for the tachykinin NK₂ receptors is 134x higher than the mean C_{max} of relugolix at steady state (46.4 ng/mL) at the recommended dosing regimen.

5.3.3. Safety Pharmacology

Data (presented by FDA):

Cardiovascular system

In vitro: In HEK293 cells stably expressing hERG channel, TAK-385 (0, 0.3, 3 and 30 μ g/mL) inhibited the hERG current at ≥ 3 μ g/mL with an IC₅₀ value of 9.7 μ g/mL. As expected, positive control (0.051 μ g/mL E-4031) inhibited hERG current, exhibiting a residual current rate of 7.5%.

In vivo: The effects of TAK-385 on the cardiovascular system were evaluated in telemetered conscious male monkeys (n=4) using a crossover design. Monkeys were administered a single oral dose of TAK-385 at 0, 30, 100 or 300 mg/kg, with a 7-day interval between doses. Results showed TAK-383 at ≥ 100 mg/kg induced a statistically significant increase in QT (up to 51 msec) and QTc (up to 47 msec) intervals at 8 h post-treatment compared to vehicle. Prolonged QTc interval (up to 26 msec; $P \leq 0.05$) was also noted 1 h post-treatment at ≥ 100 mg/kg. Statistically significant differences in PR interval were also noted 4 or 24 h after dosing with ≥ 30 mg/kg, but differences were minimal (up to 4 msec versus vehicle).

Central nervous system:

Male rats (n=6/group) were administered a single oral dose of TAK-386 at doses of 0, 200, 600 and 2000 mg/kg. Functional observation battery parameters (home cage and handling observations, body temperature, open field observations and sensorimotor reflexes) were monitored at pre-dose and 1, 2, 4, 8 and 24 h post-dose. All animals survived. Observed parameters were limited to cloudy urine at 2000 mg/kg noted in 1/6 animals at 4 and 24 h post-dose and 5/6 animals at 8 h post-dose. In conclusion, doses up to 2000 mg/kg TAK-385 did not alter central nervous system parameters but caused cloudy urine at maximum dose tested.

Respiratory system:

Male rats (n=8/group) were administered a single oral dose of TAK-385 at 0, 200, 600 and 2000 mg/kg. Using whole body plethysmography, results showed up to 2000 mg/kg

TAK-385 had no adverse effects on respiratory rate, tidal volume, minute volume and enhanced pause at time points tested (pre-dose and 1, 2, 4, 8 and 22 hours post-dose).

The Applicant's Position:

In HEK-293 cells that stably expressed the human ether-à-go-go-related gene (hERG) channel, relugolix demonstrated an inhibitory effect on hERG current with an IC_{50} of 9.7 $\mu\text{g/mL}$ (TAK-385-00072), which is ~123-fold higher than the mean total C_{max} of relugolix at steady state after administration of 120 mg doses. The effects of a single dose of 100 or 300 mg/kg relugolix on heart rate, blood pressure, and electrocardiogram (ECG) parameters were investigated in cynomolgus monkeys using a telemetry system. No test article-related changes were noted in the systolic, diastolic, and mean blood pressures, heart rate, PR interval, or QRS duration at any dose at any time point (TAK-385-00071). Prolongation of the QTc interval was noted 4 and 8 hours postdose at both 100 and 300 mg/kg (estimated C_{max} at 100 mg/kg ~4.0 $\mu\text{g/mL}$ based on exposure in the 4-week monkey toxicity study, ~51-fold higher than the human C_{max} associated with the anticipated clinical dose of 120 mg once daily).

Relugolix had no effects on the central nervous system (CNS) or acute effects on the respiratory system in male Sprague-Dawley rats administered single oral doses up to 2000 mg/kg (TAK-385-00069, TAK-385-00070). The C_{max} associated with the no observable effect level (NOEL) for CNS and respiratory effects in rats (2000 mg/kg) is ~95-fold higher than the mean C_{max} of relugolix at steady state associated with the anticipated clinical dose of 120 mg once daily.

The FDA's Assessment:

FDA agrees with the Applicant's conclusion of the hERG assay and single-dose safety pharmacology studies mentioned above but differs in the calculated exposure multiples, as FDA used the recommended PK parameters provided by the clinical pharmacology team.

Toxicokinetics were not conducted in the cardiovascular safety study; thus, TK parameters from the 4-week monkey study were used to determine exposure multiples. The estimated C_{max} at 100 mg/kg, where changes were noted, is 90 times the human C_{max} at steady state. While no adverse effects were noted on central nervous system and respiratory parameters with TAK-385, cloudy urine at 2000 mg/kg were noted in 1/6 animals at 4 and 24 h post-dose and 5/6 animals at 8 h post-dose in Study# TAK-385-00069. Toxicokinetics were not conducted in the rat safety studies. The C_{max} in the 4-week rat study at the 2000 mg/kg dose, was 262 times the human C_{max} at the recommended administration.

5.4. ADME/PK

The Applicant's Position:

Relugolix demonstrated moderate intrinsic permeability in vitro in colorectal adenocarcinoma cells (Caco-2) cell monolayers and is a substrate for P-gp (efflux ratio = 16.4). The active efflux of relugolix in Caco-2 cells is mediated by P-gp, not breast cancer resistance protein (BCRP) (b) (4). Following oral administration of single doses of relugolix to fasted rats (TAK-385/00076 and TAK-385/12713) and monkeys (TAK-385/00077 and TAK-385/12714), relugolix was rapidly absorbed (time to maximum plasma concentration [t_{max}] ~1 to 3 hours). Similar to humans, oral bioavailability of relugolix was low (< 10%) in both rat and monkey, likely attributable to limited intestinal absorption as a P-gp substrate, and to a lesser extent first pass metabolism by cytochrome P450 (CYP)3A4. Oral exposure to relugolix was reduced in fed monkeys compared to those in the fasted state.

Following oral administration to rats, relugolix is widely distributed into most tissues (TAK-385/00081, TAK-385/00082, TAK-385/00083, TAK-385/12448, TAK-385/12449). Plasma protein binding ranged from 57% to 83% across species tested (80% to 83% in mouse, 74% to 76% in rat, 57% to 59% in monkey, and 68% to 71% in human; TAK-385/00084). At 4 hours postdose in both male (TAK-385/00081) and female rats (TAK-385/00082), the maximum tissue concentrations in male rats were generally observed in tissues associated with relugolix absorption, metabolism, and elimination.

The metabolic profiles of relugolix were qualitatively similar across species both in vitro and in vivo. The liver and gastrointestinal tract are the primary sites of metabolism for relugolix. There are no major metabolites identified. Relugolix is metabolized to Metabolite-A by O-demethylation (CYP3A4), to Metabolite-B by hydroxylation (CYP2C8), and to Metabolite-C by N-demethoxylation (intestinal microflora) (TAK-385/00041, TAK-385/13009, TAK-385/12402).

After oral administration of relugolix to rats (TAK-385/00076 and TAK-385/12713) and monkeys (TAK-385/00077 and TAK-385/12714), relugolix was eliminated with a terminal phase half-life of 2.1 and 5.6 hours, respectively. The primary route of excretion of total radioactivity was via feces (> 96% and > 90% of the dose, respectively, for rats and monkeys) (TAK-385/00074 and TAK-385/00079). Approximately 97.8% and 97.0% of the cumulative total radioactive dose was recovered postdose in rats (by 72 hours) and monkeys (by 168 hours), respectively. Following oral doses of relugolix, most of the dose-related material was excreted as metabolites with unchanged relugolix accounting for ≤ 8.0% of the total dose in urine, feces, or bile of rats (TAK-385/00088). In rat feces, Metabolite-C was the most predominant component, accounting for > 59% of the oral dose in rats. Similar results were noted in human and monkey feces where Metabolite-C was the predominant component, accounting for ~40% and ~45% of the total radioactive dose, respectively.

At clinically relevant concentrations, relugolix was not a direct time-dependent inhibitor of the major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4) or an inducer of CYP1A2 or CYP2B6, although relugolix was a direct inhibitor and inducer of CYP3A. In vitro, relugolix was an inhibitor of BCRP, and less potently P-

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gp, but did not cause inhibition of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, or bile salt export pump at clinically relevant concentrations.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusion of the study results. Additional noteworthy study data, TK data and comments on Applicant's summary are provided below. See the clinical pharmacology Section 6 for information regarding human data, in vitro drug interaction studies and effects of other drugs on relugolix.

Data (presented by FDA):

Type of Study	Major Findings																																													
Absorption																																														
Plasma concentrations of TAK-385 in monkeys after a single oral and intravenous administration of TAK-385 (Study# TAK-385-00077)	<p>Monkey Following a single IV or oral dose administered under fasted or fed conditions to male monkeys:</p> <table border="1"> <thead> <tr> <th>Dose, route</th> <th>Feeding</th> <th>C_{max} ng/mL</th> <th>T_{max} h</th> <th>T_{1/2} h</th> <th>AUC_{0-48h} ng.h/mL</th> <th>CL L/h/kg</th> <th>V_{ss} L/kg</th> <th>BA %</th> </tr> </thead> <tbody> <tr> <td rowspan="2">1 mg/kg Oral</td> <td>Fasted</td> <td>4</td> <td>2</td> <td>5.6</td> <td>25</td> <td>ND</td> <td>ND</td> <td>6.9</td> </tr> <tr> <td>Fed</td> <td>0.7</td> <td>0.25</td> <td>ND</td> <td>1.2</td> <td>ND</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>0.2 mg/kg IV</td> <td>Fasted</td> <td>61</td> <td>ND</td> <td>7.2</td> <td>77</td> <td>3</td> <td>20</td> <td>ND</td> </tr> </tbody> </table> <p>The C_{max} after IV administration denotes C_{5min}</p>	Dose, route	Feeding	C _{max} ng/mL	T _{max} h	T _{1/2} h	AUC _{0-48h} ng.h/mL	CL L/h/kg	V _{ss} L/kg	BA %	1 mg/kg Oral	Fasted	4	2	5.6	25	ND	ND	6.9	Fed	0.7	0.25	ND	1.2	ND	ND	ND	0.2 mg/kg IV	Fasted	61	ND	7.2	77	3	20	ND										
Dose, route	Feeding	C _{max} ng/mL	T _{max} h	T _{1/2} h	AUC _{0-48h} ng.h/mL	CL L/h/kg	V _{ss} L/kg	BA %																																						
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Pharmacokinetics of single dose relugolix studies (Study# TAK-385-12713 & TAK-385-12714)	<p>Summary of PK parameters after a single oral administration under fasted conditions</p> <table border="1"> <thead> <tr> <th>Dose mg/kg</th> <th>T_{max} h</th> <th>C_{max} ng/mL</th> <th>T_{1/2} h</th> <th>AUC ng.h/mL</th> </tr> </thead> <tbody> <tr> <td colspan="5">Rat (n=3): Study# TAK-385-12713</td> </tr> <tr> <td>5</td> <td>2.7</td> <td>31</td> <td>2.4</td> <td>107</td> </tr> <tr> <td>12</td> <td>3.3</td> <td>46</td> <td>6</td> <td>298</td> </tr> <tr> <td>30</td> <td>3.3</td> <td>429</td> <td>5</td> <td>1681</td> </tr> <tr> <td colspan="5">Monkey (n=4): Study# TAK-385-12714</td> </tr> <tr> <td>1</td> <td>0.8</td> <td>45</td> <td>5.5</td> <td>181</td> </tr> <tr> <td>5</td> <td>1.6</td> <td>367</td> <td>6.7</td> <td>2093</td> </tr> <tr> <td>20</td> <td>1.8</td> <td>2081</td> <td>5.4</td> <td>14932</td> </tr> </tbody> </table>	Dose mg/kg	T _{max} h	C _{max} ng/mL	T _{1/2} h	AUC ng.h/mL	Rat (n=3): Study# TAK-385-12713					5	2.7	31	2.4	107	12	3.3	46	6	298	30	3.3	429	5	1681	Monkey (n=4): Study# TAK-385-12714					1	0.8	45	5.5	181	5	1.6	367	6.7	2093	20	1.8	2081	5.4	14932
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Distribution																																														
Concentrations of radioactivity in the tissues of rats after a single oral administration of [¹⁴ C]TAK-385 (Study# TAK-385-00081)	<p>Rat Following a 5 mg/kg single oral administration of [¹⁴C]TAK-385 to fasted male rats (n=3/timepoint): -The tissues with the highest absorbed doses of radiation were liver, intestine, thyroid, stomach and pituitary gland.</p>																																													

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Type of Study	Major Findings
Concentrations of radioactivity in the tissues of pigmented rats after a single oral administration of [¹⁴ C]TAK-385 (Study# TAK-385-00083)	<p>Rat</p> <p>Following a 5 mg/kg single oral administration of [¹⁴C]TAK-385 to fasted male Long Evans rats (n=3/timepoint):</p> <ul style="list-style-type: none"> -Radioactivity in the eyes, mainly localized to the melanin rich tissues (anterior and posterior parts of eye), was detected at 4 h post-dose and sustained for up 12-weeks post-dose
Feto-placental transfer of radioactivity after single oral administration of [¹⁴ C]TAK-385 to pregnant rats (Study# TAK-385-12711)	<p>Rat</p> <p>Following a 30 mg/kg single oral administration of [¹⁴C]TAK-385 to fasted female rats on the 18th day of pregnancy (n=3/timepoint):</p> <ul style="list-style-type: none"> -Maximum radioactivity was distributed at 4h to placenta (1.932 µg equiv/mL), 8 h to fetuses (0.105 µg equiv/mL) and fetal plasma (0.031 µg equiv/mL) and 24 h to amniotic fluid (0.019 µg equiv/mL)
Excretion	
Urinary, fecal and expiratory excretion of radioactivity in rats after a single oral administration of [¹⁴ C]TAK-385 (Study# TAK-385/00074)	<p>Rat</p> <p>Following a 5 mg/kg single oral administration of [¹⁴C]TAK-385 to fasted male rats (n=3):</p> <ul style="list-style-type: none"> -Fecal excretion was the major route of elimination of relugolix, with a up to 96% cumulative excretion of radioactivity occurring 24-72 h post-dosing. - By 72 hrs post-dose, approximately 97.8% of the cumulative total radioactive dose was recovered -Metabolite profiles using urine and feces samples from this study were analyzed in Study# TAK-385-00088. Results showed feces contained highest % radioactivity with metabolite-C being the major component, comprising of 62% radioactivity and an excretion ratio of 59% of the dose. TAK-385 and metabolite-B were detected in excretion ratios of 8% and 3% of the dose, respectively. In urine, relugolix was the major component comprising of 92% of radioactivity and excretion ratio of 1.2% of the dose.

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Type of Study	Major Findings
<p>Plasma concentrations and excretion of radioactivity in monkeys after single oral and intravenous administration of [¹⁴C]TAK-385 (Study# TAK-385/00079)</p>	<p>Monkey Male monkeys (n=2) under fasted conditions were used. -Following a single oral dose of 1 mg/kg, fecal excretion was the major route of elimination, with 92% in feces and 5% in urine. Approximately 97% of total radioactivity was recovered by 168 h post-dose -Following a single intravenous dose of 0.2 mg/kg, fecal excretion was major route of elimination, with 69% in feces and 24% in urine. Approximately 93% of total radioactivity was recovered by 168 h post-dose. - Metabolite profiles using urine and feces samples from this study (oral administration) were analyzed in Study# TAK-385-00089. Results showed feces contained highest % radioactivity with metabolite-C being the major component, comprising of 50% radioactivity and an excretion ratio of 45% of the dose. TAK-385 and metabolite-A were detected in excretion ratios of 2.3% and 0.2% of the dose, respectively. In urine, relugolix was the major component comprising of 56% of radioactivity and excretion ratio of 2.4% of the dose.</p>
<p>Lacteal secretion of [¹⁴C]TAK-385 in rats (Study# TAK-385-1272)</p>	<p>Rat Following a single oral administration of 30 mg/kg [¹⁴C]TAK-385 to fasted lactating female rats (n=5) at 14 days after parturition: -Maximum mean levels of radioactivity were detected at 2 h post-administration in both plasma (0.441± 0.327 µg equiv/mL) and milk (4.262 ± 5.192 µg equiv./mL). -Radioactivity decreased overtime. At 48 h, mean levels were below the limit of quantification and 0.057 µg ± 0.038 equiv/mL for plasma and milk, respectively.</p>
<p>Drug Interactions In Study# TAK-385-13265, relugolix inhibited MATE-1, MATE2-K and BCRP-mediated transport of radiolabeled substrates with IC₅₀ values of 10.9, 3.75 and 24.9 µM, respectively.</p>	

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Type of Study	Major Findings																																																														
<p>TK data from general toxicology studies Twenty-six oral gavage toxicity study of TAK-385 in rats (Study# TAK-385-000145)</p>	<p>Rat Accumulation: 1.3x - 19x, C_{max} and AUC exposure in Day 177 versus Day 1 Dose proportionality: A greater than dose proportional increase at all dose levels</p> <table border="1" data-bbox="659 390 1300 993"> <thead> <tr> <th>Day</th> <th>Sex</th> <th>Dose (mg/kg)</th> <th>C_{max} (ng/mL)</th> <th>AUC_(0-24h) (ng·hr/mL)</th> </tr> </thead> <tbody> <tr> <td rowspan="6">1</td> <td rowspan="3">M</td> <td>10</td> <td>2</td> <td>13</td> </tr> <tr> <td>30</td> <td>65</td> <td>350</td> </tr> <tr> <td>100</td> <td>631</td> <td>2937</td> </tr> <tr> <td rowspan="3">F</td> <td>300</td> <td>1129</td> <td>6155</td> </tr> <tr> <td>10</td> <td>7</td> <td>23</td> </tr> <tr> <td>30</td> <td>94</td> <td>296</td> </tr> <tr> <td rowspan="6">177</td> <td rowspan="3">M</td> <td>100</td> <td>622</td> <td>2771</td> </tr> <tr> <td>300</td> <td>1128</td> <td>6754</td> </tr> <tr> <td>10</td> <td>38</td> <td>212</td> </tr> <tr> <td rowspan="3">F</td> <td>30</td> <td>247</td> <td>1653</td> </tr> <tr> <td>100</td> <td>875</td> <td>7152</td> </tr> <tr> <td>300</td> <td>2911</td> <td>34077</td> </tr> <tr> <td rowspan="4"></td> <td rowspan="2">M</td> <td>10</td> <td>62</td> <td>249</td> </tr> <tr> <td>30</td> <td>257</td> <td>1534</td> </tr> <tr> <td rowspan="2">F</td> <td>100</td> <td>1200</td> <td>6109</td> </tr> <tr> <td>300</td> <td>2541</td> <td>26951</td> </tr> </tbody> </table>	Day	Sex	Dose (mg/kg)	C _{max} (ng/mL)	AUC _(0-24h) (ng·hr/mL)	1	M	10	2	13	30	65	350	100	631	2937	F	300	1129	6155	10	7	23	30	94	296	177	M	100	622	2771	300	1128	6754	10	38	212	F	30	247	1653	100	875	7152	300	2911	34077		M	10	62	249	30	257	1534	F	100	1200	6109	300	2541	26951
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<p>Thirty-nine week oral gavage toxicity study of TAK-385 in monkeys (Study# TAK-385-00144)</p>	<p>Monkey Accumulation: 2x – 2.8x, C_{max} and AUC exposure at 1.5 mg/kg dose only (Day 273 vs Day 1) Dose proportionality: A greater than dose proportional increase at all doses.</p> <table border="1" data-bbox="659 1157 1300 1759"> <thead> <tr> <th>Day</th> <th>Sex</th> <th>Dose (mg/kg)</th> <th>C_{max} (ng/mL)</th> <th>AUC₍₀₋₂₄₎ (ng·hr/mL)</th> </tr> </thead> <tbody> <tr> <td rowspan="6">1</td> <td rowspan="3">M</td> <td>1.5</td> <td>20</td> <td>103</td> </tr> <tr> <td>5</td> <td>181</td> <td>717</td> </tr> <tr> <td>15</td> <td>1002</td> <td>4173</td> </tr> <tr> <td rowspan="3">F</td> <td>50</td> <td>2816</td> <td>16813</td> </tr> <tr> <td>1.5</td> <td>26</td> <td>91</td> </tr> <tr> <td>5</td> <td>213</td> <td>932</td> </tr> <tr> <td rowspan="6">273</td> <td rowspan="3">M</td> <td>15</td> <td>608</td> <td>3021</td> </tr> <tr> <td>50</td> <td>2810</td> <td>16521</td> </tr> <tr> <td>1.5</td> <td>56</td> <td>264</td> </tr> <tr> <td rowspan="3">F</td> <td>5</td> <td>230</td> <td>1087</td> </tr> <tr> <td>15</td> <td>990</td> <td>5046</td> </tr> <tr> <td>50</td> <td>3049</td> <td>19906</td> </tr> <tr> <td rowspan="4"></td> <td rowspan="2">M</td> <td>1.5</td> <td>50</td> <td>190</td> </tr> <tr> <td>5</td> <td>334</td> <td>1554</td> </tr> <tr> <td rowspan="2">F</td> <td>15</td> <td>895</td> <td>5349</td> </tr> <tr> <td>50</td> <td>2473</td> <td>19369</td> </tr> </tbody> </table>	Day	Sex	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	1	M	1.5	20	103	5	181	717	15	1002	4173	F	50	2816	16813	1.5	26	91	5	213	932	273	M	15	608	3021	50	2810	16521	1.5	56	264	F	5	230	1087	15	990	5046	50	3049	19906		M	1.5	50	190	5	334	1554	F	15	895	5349	50	2473	19369
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Type of Study	Major Findings																																																											
<p>TK data from carcinogenicity studies Twenty-four month oral gavage carcinogenicity study of TAK-385 in mice (Study# TAK-385-10217)</p>	<p>Mice Accumulation: No; a decrease (0.12x to 0.7x) in C_{max} and AUC exposure was noted at 10 and 30 mg/kg/day Dose proportionality: A greater than dose proportional increase at all doses.</p> <table border="1"> <thead> <tr> <th>Day</th> <th>Sex</th> <th>Dose (mg/kg)</th> <th>C_{max} (ng/mL)</th> <th>AUC₍₀₋₂₄₎ (ng·hr/mL)</th> </tr> </thead> <tbody> <tr> <td rowspan="6">1</td> <td rowspan="3">M</td> <td>10</td> <td>541</td> <td>1277</td> </tr> <tr> <td>30</td> <td>3035</td> <td>8331</td> </tr> <tr> <td>100</td> <td>7358</td> <td>26791</td> </tr> <tr> <td rowspan="3">F</td> <td>10</td> <td>470</td> <td>927</td> </tr> <tr> <td>30</td> <td>2666</td> <td>6340</td> </tr> <tr> <td>100</td> <td>7425</td> <td>27446</td> </tr> <tr> <td rowspan="6">365</td> <td rowspan="3">M</td> <td>10</td> <td>66</td> <td>327</td> </tr> <tr> <td>30</td> <td>1738</td> <td>3371</td> </tr> <tr> <td>100</td> <td>7255</td> <td>23954</td> </tr> <tr> <td rowspan="3">F</td> <td>10</td> <td>278</td> <td>659</td> </tr> <tr> <td>30</td> <td>1359</td> <td>3974</td> </tr> <tr> <td>100</td> <td>9191</td> <td>32279</td> </tr> </tbody> </table>	Day	Sex	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	1	M	10	541	1277	30	3035	8331	100	7358	26791	F	10	470	927	30	2666	6340	100	7425	27446	365	M	10	66	327	30	1738	3371	100	7255	23954	F	10	278	659	30	1359	3974	100	9191	32279												
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<p>Twenty-four-month oral gavage carcinogenicity study of TAK-385 in rats (Study# TAK-385-10218)</p>	<p>Rats Accumulation: 1.7x to 26x, C_{max} and AUC exposure in Day 359 versus Day 1 Dose proportionality: A greater than dose proportional increase at all doses.</p> <table border="1"> <thead> <tr> <th>Day</th> <th>Sex</th> <th>Dose (mg/kg)</th> <th>C_{max} (ng/mL)</th> <th>AUC₍₀₋₂₄₎ (ng·hr/mL)</th> </tr> </thead> <tbody> <tr> <td rowspan="8">1</td> <td rowspan="4">M</td> <td>10</td> <td>2</td> <td>14</td> </tr> <tr> <td>30</td> <td>109</td> <td>505</td> </tr> <tr> <td>200</td> <td>795</td> <td>4747</td> </tr> <tr> <td>600</td> <td>2559</td> <td>27817</td> </tr> <tr> <td rowspan="4">F</td> <td>10</td> <td>11</td> <td>57</td> </tr> <tr> <td>30</td> <td>87</td> <td>451</td> </tr> <tr> <td>200</td> <td>887</td> <td>5847</td> </tr> <tr> <td>600</td> <td>1967</td> <td>22316</td> </tr> <tr> <td rowspan="8">359</td> <td rowspan="4">M</td> <td>10</td> <td>28</td> <td>211</td> </tr> <tr> <td>30</td> <td>247</td> <td>1467</td> </tr> <tr> <td>200</td> <td>1401</td> <td>15465</td> </tr> <tr> <td>600</td> <td>7365</td> <td>91900</td> </tr> <tr> <td rowspan="4">F</td> <td>10</td> <td>33</td> <td>133</td> </tr> <tr> <td>30</td> <td>351</td> <td>1836</td> </tr> <tr> <td>200</td> <td>2050</td> <td>18437</td> </tr> <tr> <td>600</td> <td>5668</td> <td>75632</td> </tr> </tbody> </table>	Day	Sex	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	1	M	10	2	14	30	109	505	200	795	4747	600	2559	27817	F	10	11	57	30	87	451	200	887	5847	600	1967	22316	359	M	10	28	211	30	247	1467	200	1401	15465	600	7365	91900	F	10	33	133	30	351	1836	200	2050	18437	600	5668	75632
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5.5. Toxicology

5.5.1. General Toxicology

Data (presented by FDA):

The repeat-dose toxicity studies were initially reviewed by the FDA under (b) (4), and findings are presented as in original IND or reformatted to fit the NDA review.

Study title/ number: Twenty-six weeks oral gavage toxicity study of TAK-385 in rats / TAK-385-000145

- TAK-385 caused minimal eosinophilic crystals in epithelium of epididymides and minimal foam cell infiltration, related to phospholipidosis, in testes at ≥ 100 mg/kg/day and lung at 300 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	10, 30, 100, 300 mg/kg/day
Justification of doses:	Based on mortality, severe systemic phospholipidosis and necrosis in many organs at 2000 mg/kg/day observed in a 4-week study evaluating doses of 10, 30, 300 and 2000 mg/kg/day.
Route of administration:	Oral, gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	15/sex/dose (5/sex/dose for recovery)
Age:	~6 weeks old
Satellite groups/ unique design:	5/sex/group for TK
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	One control male died on week 15 of administration. The cause of death was spontaneous lymphoid leukemia.
Clinical Signs	300 mg/kg/day: Cloudy urine noted starting on week 15 until end of study

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Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
Hematology	Unremarkable
Coagulation	Not assessed
Clinical Chemistry	Unremarkable
Urinalysis	HD: Increase in urine volume 110%
Gross Pathology	Control: Early decedent had enlargement of liver and spleen, dark red foci in the lungs and excess fluid in the abdominal cavity.
Organ Weights	Changes noted in absolute weights were small in magnitude and not significant in relative weights: 300 mg/kg/day: Males: testes, 8%; Females: liver, 10%
Histopathology Adequate battery: Yes	<u>Scheduled necropsy, end of dosing:</u> Control: evidence of large granular lymphocytic leukemia in early decedent All other histopathology findings are listed in table below. <u>Recovery:</u> Not conducted

Doses (mg/kg/day)	Males					Females				
	0	10	30	100	300	0	10	30	100	300
n	15	15	15	15	15	15	15	15	15	15
Epididymis Eosinophilic crystal, epithelial Minimal					7					
Liver Vacuolation, hepatocyte, scattered Minimal Hemorrhage, focal Minimal					1 1					
Lung Foam cell infiltration Minimal Metaplasia, osseous Minimal	5				8 2	3				6
Testes Foam cell infiltration, interstitial Minimal				7	13					
Thyroid Hypoplasia, unilateral Moderate					1					
Heart Cardiomyopathy Minimal					1					
Pituitary Hyperplasia, acinar cell, focal Minimal										1

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Study title/ number: Thirty-nine week oral gavage toxicity study of TAK-385 in monkeys with a 13 week recovery period / TAK-385-000144

- TAK-385 caused systemic phospholipidosis (increase in foamy cells, tingible body macrophages and cell vacuolation) at ≥ 1.5 mg/kg/day and increased liver enzymes at 50 mg/kg/day.

Conducting laboratory and location: (b) (4)
 GLP compliance: Yes

Methods

Dose and frequency of dosing: 1.5, 5, 15, 50 mg/kg/day
 Justification of doses: Based on liver toxicity at 100 mg/kg/day and systemic phospholipidosis at ≥ 10 mg/kg/day observed in a 4-week study evaluating doses of 10, 20 and 100 mg/kg/day.

Route of administration: Oral, gavage
 Formulation/Vehicle: 0.5% methylcellulose, 6 mg/mL citric acid
 Species/Strain: Monkey/Cynomolgus
 Number/Sex/Group: 4/sex/group (4/sex/control or HD only for recovery)

Age: 36 to 43 months
 Satellite groups/ unique design: 5/sex/group for TK
 Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	50 mg/kg/day: Cloudy urine noted starting on Week 1 until end of dosing Menses was not observed in females from Day 13 until end of dosing, which was reversible.
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable

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ECG	<p>Isolated incidences of ventricular premature contractions, atrial premature contractions and sinus arrest and A-V junctional escape beats were reported in all treated and control groups with low frequency, which were observed pre-dose and had no dose-relationship</p> <p>Statistically significant changes noted in PR were comparable to baseline or lacked a dose relationship</p>
ERG	Unremarkable
Hematology	<p><u>13 weeks:</u> 15 mg/kg/day, males: HGB and HCT (up to -8%)</p> <p><u>26 weeks:</u> 15 mg/kg/day, males: HGB, HCT and MCH (up to -8%) ≥ 15 mg/kg/day, females: reticulocyte count and/or ratio (-30%)</p> <p><u>39 weeks:</u> ≥ 15 mg/kg/day, females: neutrophil count and ratio (up to -54%) and lymphocyte ratio (up to 37%) 50 mg/kg/day: reticulocyte count and/or ratio (up to -36%)</p> <p><u>Recovery:</u> 50 mg/kg/day, females: HGB (-6%)</p>
Coagulation	Unremarkable
Clinical Chemistry	<p><u>Week 13</u> ≥15 mg/kg/day males: IP (up to -18%) 50 mg/kg/day: AST (69%), ALT (397% M and 294% F) and CHOL (22% M and 35% F)</p> <p><u>Week 26</u> ≥5 mg/kg/day males: IP (up to -27%) 50 mg/kg/day: AST (80% M and 62% F), ALT (471% M and 322% F) and CHOL (28% M and 33% F); and PL (25%) and CL (2%) in females</p> <p><u>Week 39</u> ≥5 mg/kg/day males: IP (up to -21%) 50 mg/kg/day: AST (100% M and 31% F), ALT (548% M and 219% F), CHOL (42% M and 34% F) and CL (3% M and 2% F); and PL (25%) in males</p> <p>While other parameters also showed statistically significant changes versus control, they were similar to baseline levels and/or control levels changed influencing comparisons. Parameters exhibited reversibility.</p>
Urinalysis	50 mg/kg/day: Cloudy urine
Gross Pathology	50 mg/kg/day: Liver, dark, brownish change (3/4M; 4/4F)
Organ Weights	<p>Ovary: reversible decrease (up to -59%) at ≥ 1.5 mg/kg/dose</p> <p>Other changes noted lacked histological correlates or were noted only at recovery</p>

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<p>Histopathology Adequate battery: Yes</p>	<p><u>Scheduled necropsy, end of dosing:</u> See main study histopathology findings in table below.</p> <p>In addition, slight mononuclear cell infiltration was noted in heart, lung and stomach in treatment groups, as well as controls.</p> <p><u>Recovery:</u> See recovery histopathology findings below.</p>
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M: male; F: female

-: indicates reduction in parameter relative to control

Main study histopathology findings:

Doses (mg/kg/day)	Males					Females				
	0	1.5	5	15	50	0	1.5	5	15	50
n	4	4	4	4	4	4	4	4	4	4
Bone marrow (sternum) Increased in tingible body macrophage Slight				2	3				3	4
Bone marrow (femur) Increased in tingible body macrophage Slight				2	3				3	4
Spleen Increased in tingible body macrophage Slight Enlargement of germinal center Slight				3	4				1	3
		2	2	1	1			1		
Lymph node, submandibular Foam cell in lymphatic sinus Slight Increased in tingible body macrophage Slight			1	3	4				3	3
					2				3	2
Lymph node, mesenteric Foam cell in lymphatic sinus Slight Increased in tingible body macrophage Slight		1	2	3	4		2	4	4	3
				1	2				1	2
Submandibular gland Mononuclear cell infiltration Slight								1	1	2
Stomach Hemorrhage in mucosa Slight Increased in tingible body macrophage in lymphoid follicle Slight Vacuolation in parietal cell Slight		3	3		1	1	2		1	
				3	2			3	3	2
			1	2	4			1	4	3
Duodenum										

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Doses (mg/kg/day)	Males					Females				
	0	1.5	5	15	50	0	1.5	5	15	50
n	4	4	4	4	4	4	4	4	4	4
Increased in tingible body macrophage in lymphoid follicle					2					
Pigment deposition					1					
Hemorrhage in mucosa										1
Ileum										
Increased in tingible body macrophage in lymphoid follicle					1					1
Cecum										
Increased in tingible body macrophage in lymphoid follicle									1	1
Pigment deposition										1
Colon										
Hemorrhage in mucosa		1	1		3					
Increased in tingible body macrophage in lymphoid follicle					3			1		
Pigment deposition			1		1					1
Rectum										
Increased in tingible body macrophage in lymphoid follicle										1
Liver										
Bile thrombus					2					1
Fatty change of hepatocyte, diffuse					2					3
Subcapsular fibrosis				1	1					
Yellowish brown pigment deposition in Kupffer cell		1								
					1					
					1					3
					2					1
Pancreas										
Hemorrhage in islet			1	2	1					
Urinary bladder										

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Doses (mg/kg/day)	Males					Females				
	0	1.5	5	15	50	0	1.5	5	15	50
n	4	4	4	4	4	4	4	4	4	4
Mononuclear cell infiltration into submucosa Slight				1						
Thyroid Mononuclear cell infiltration Slight		1			1				1	
Adrenal Hyperplasia of cortical cell, focal Slight										1
Uterus Pigment deposition in mucosa Moderate									1	
Ovary Decrease of corpus luteum							3	4	4	

Recovery histopathology findings:

Doses (mg/kg/day)	Males		Females	
	0	50	0	50
n	4	4	4	4
Spleen Enlargement of germinal center Slight				1
Lymph node, submandibular Pigment deposition in medulla Slight				1
Lymph node, mesenteric Foam cell in lymphatic sinus Slight		1		
Pigment deposition in medulla Slight		1		1
Stomach Hemorrhage in mucosa Slight		1		
Vacuolation in parietal cell Slight				1
Duodenum Mononuclear cell infiltration into lamina propria of mucosa Slight		1		
Cecum Hemorrhage in mucosa Slight		1		
Liver Fatty change of hepatocyte, diffuse Slight		2		
Mononuclear cell foci				

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	Males		Females	
	0	50	0	50
Doses (mg/kg/day)	0	50	0	50
n	4	4	4	4
Yellowish brown pigment deposition in Kupffer cell		1		3
Slight		1		
Moderate		1		2
Severe				1
Pancreas				
Hemorrhage in islet				
Slight		1		1
Urinary bladder				
Mononuclear cell infiltration into submucosa				
Slight		1		
Thyroid				
Increase in large follicle				
Moderate		1		
Cerebrum				
Pigment deposition				
Slight				1

General toxicology; additional studies

Study title/ number: Thirteen-week oral gavage range-finding toxicity study of TAK-385 in mice / TAK-385-00119

Daily oral treatment to mice at doses up to 2000 mg/kg/day for 13 weeks was generally tolerated. Key study findings observed at 2000 mg/kg/day were increased body weight and food consumption; decreased red blood cell parameters associated with increased spleen weight and increased extramedullary hematopoiesis; increased granulocyte hematopoietic cells in bone marrow of femur and sternum; decreased kidney weight associated with minimal necrosis of renal tubular epithelium and increased renal tubular basophilia; inflammatory cell infiltration and hyperplasia of mucosal epithelium in female cecum and in colon of both sexes.

Study title/ number: Four-week gavage range-finding toxicity study of TAK-385 in mice / TAK-385-00073

Mice tolerated doses up to 2000 mg/kg/day TAK-385. Histopathology was limited to liver, kidneys (only tissues examined at all dose levels), heart, lungs, spleen, cecum, testes and upper incisors in control and 2000 mg/kg/day groups only. Key study findings at 2000 mg/kg/day were white colored stools (3/4 females on Day 0 only), large cecum with fecal retention (all animals) and renal tubules necrosis and increased incidence of tubular basophilia.

Study title/ number: Four-week gavage toxicity of TAK-385 in rats / TAK-385-00107

Doses up to 2000 mg/kg/day were evaluated. Deaths were reported at 2000 mg/kg/day (8 males; 5 females), starting on Day 5 and up to Day 30. TAK-385 caused systemic phospholipidosis, associated with vacuolation, atrophy and/or necrosis of majority of organ/tissues at high dose groups. Regeneration and dilatation of the renal tubules hyaline casts, inflammatory cell infiltration, hyaline droplets in the renal tubules of up to mild severity were noted at high dose.

Study title/ number: Four-week gavage toxicity of TAK-385 in monkeys / TAK-385-00102

Monkeys tolerated doses up to 100 mg/kg/day. Key study findings included drug-related vomiting, cloudy urine, systemic phospholipidosis, QT prolongation but was not evident in QTc, increased supraventricular premature contractions and elevated liver enzymes (AST, up to 4.3x; ALT, up to 15.7x at 100 mg/kg/day). Systemic phospholipidosis was associated with increased tingible body macrophages in the bone marrow, thymus, spleen, lymph nodes, stomach and/or gastrointestinal lymphoid tissue; increased foamy cell infiltrates in submandibular and mesenteric lymph nodes at ≥ 10 mg/kg/day; vacuolization of parietal cells in stomach at ≥ 20 mg/kg/day; and foam cell accumulation in the lungs and vacuolization of acinar cells in pancreas at 100 mg/kg/day.

The Applicant's Position:

Toxicology studies were performed with relugolix and include single-dose toxicity studies in rats and repeat-dose toxicity studies in mice (up to 13 weeks duration), rats (up to 26 weeks duration), and monkeys (up to 39 weeks duration). Relugolix was highly species specific as the binding affinity for human and monkey GnRH receptors was approximately 19,000- and 24,000-fold more potent, respectively, than for rat GnRH receptors. Although relugolix demonstrates a lower affinity for rat GnRH receptors, rats are an appropriate model to evaluate potential chemical-based or off-target effects of relugolix.

For relugolix, the principal adverse effects in toxicity studies involved findings in the liver (liver enzyme elevations with and without accompanying histopathological correlates) and kidney and mortality at high doses/exposures. Additionally, phospholipidosis (PLD) was observed in various tissues following repeated relugolix administration in rats and monkeys. Phospholipidosis by itself is not considered a manifestation of toxicity and no significant adverse effects were associated with PLD alone in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. In general, the systemic exposures at the no observed adverse effect level (NOAEL) in animal toxicity studies of relugolix are significantly higher than the expected clinical exposures.

In the 39-week monkey repeat-dose toxicity study, the NOAEL for liver toxicity is considered to be 15 mg/kg/day in both sexes, which is associated with a mean combined sex end-of-study area under the concentration-time curve from time 0 to 24

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hours (AUC₀₋₂₄) of 5198 ng.h/mL and is ~ 9.3-fold higher than the exposure humans associated with the anticipated clinical dose of 120 mg once daily. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. Therefore, the relugolix toxicology program supports the careful conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5198 ng.hr/mL) for liver toxicity in monkeys (most sensitive species).

The FDA's Assessment:

The Applicant uses terminologies such as “potent” and “highly specific” to describe the study results; these terms should be avoided as they are vague, subjective and promotional.

The FDA generally agrees with the Applicant's conclusion. General toxicology studies indicate monkeys were the most sensitive species, most likely reflecting the species binding affinity of relugolix to monkey versus rat GnRH receptors. Liver toxicity (elevated liver enzymes, associated with bile plug formation, diffuse fatty change of hepatocyte, mononuclear cell foci and yellowish-brown pigment deposition in Kupffer cells) occurred in monkeys with 50 mg/kg/day relugolix (53 times the human exposure at the human recommended dose based on AUC). Reversibility was noted for increased liver enzymes and bile plugs but other liver histopathology changes were still noted at end of recovery. Phospholipidosis in multiple organs in repeat-dose studies was observed in both rats (≥ 100 mg/kg) and monkey (≥ 1.5 mg/kg), which are 18 times and 0.6 times, respectively, the clinical exposure at the human recommended dose based on AUC. In the 13-week study in mice and 4-week rat study, up to mild kidney toxicity was noted at 2000 mg/kg/day. The binding affinity of relugolix to mice GnRH receptors is unknown.

Based on histological findings, relugolix effects on male reproductive organs were limited to rats but were related to phospholipidosis (minimal eosinophilic crystals in epithelium of epididymides and minimal foam cell infiltration in testes at ≥ 100 mg/kg/day) rather than disruption of pituitary-gonadal axis. No effects in male reproductive organs were noted in male monkeys with relugolix. Nevertheless, it is expected for relugolix to affect fertility based on its mechanism of action.

5.5.2. Genetic Toxicology

Data (presented by FDA):

In vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/number: Bacterial reversion assay with TAK-385/TAK-385-00093

Key Study Findings:

- TAK-385 was not mutagenic under the conditions tested.

GLP compliance: Yes

Test system: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and Escherichia coli Wp2_{uvrA}; up to 5000 µg/plate; +/- S9
Study is valid: Yes

In vitro Assays in Mammalian Cells

Study title/number: Cytogenetic assay with TAK-385 in Chinese Hamster Lung (CHL) cells /TAK-385-00068

Key Study Findings:

- TAK-385 did not induce chromosomal aberrations in CHL cells.

GLP compliance: Yes

Test system: CHL cells; up to 400 µg/plate; +/- S9

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Micronucleus assay with TAK-385 in rats/ TAK-385-00094

Key Study Findings:

- TAK-385 was not clastogenic under the conditions tested

GLP compliance: Yes

Test system: Rat/Sprague-Dawley (males only), bone marrow micronuclei; two oral doses (24 h apart) of 0, 500, 1000, 2000 mg/kg; collection 24 hour after the last dose

Study is valid: Yes

The Applicant's Position:

Relugolix was negative in a bacterial reverse mutation (Ames) assay (TAK-385/00093), in vitro chromosomal aberration assay (TAK-385/00068), and rat in vivo micronucleus assay (TAK-385/00094). The results indicate that relugolix does not present a genotoxic risk to humans.

The FDA's Assessment:

Genetic toxicology studies were reviewed under (b) (4). The FDA agrees with the Applicant's conclusion for the active pharmaceutical ingredient; however, we note that the impurity and degradant (b) (4) in the drug substance and drug product was shown to be mutagenic in bacteria. See Section 5.5.5. for further details.

5.5.3. Carcinogenicity

The Applicant's Position:

Relugolix was not carcinogenic in 2-year carcinogenicity studies in mouse (highest dose = 100 mg/kg/day; week 53 mean combined sex area under the concentration-time curve from time zero to 24 hours [AUC₀₋₂₄] = 28,117 ng.h/mL represents a ~51-fold

Relugolix

multiple of human exposure at 120 mg, once daily) or rat (highest dose = 600 mg/kg/day; week 52 mean combined sex $AUC_{0-24} = 83,766$ ng.h/mL, which represents a ~151-fold multiple of human exposure at 120 mg, once daily) (TAK-385/10217 and TAK-385/10218).

The FDA's Assessment:

The carcinogenicity study protocol design and results were reviewed by the Executive Carcinogenicity Assessment Committee (ECAC) at FDA under (b) (4), respectively. Of note, the relevancy of the rat model due to low binding was not discussed in these reviews. The rat model may not address if the pharmacodynamic effect of relugolix can lead to secondary malignancies, but these studies can evaluate the carcinogenic potential of the off-target effects of relugolix and its metabolites or impurities. The FDA agrees with the Applicant's conclusions, except for the human exposure multiples. TAK-385 was evaluated at doses up to 100 mg/kg/day in mice and up to 600 mg/kg/day in rats in the 2-year carcinogenicity studies. In both studies, a statistically significant dose-related decrease in survival across control and treated groups was noted in males but not in females. Pairwise comparisons showed statistically significant increases in mortality in the treated groups compared to control group in male rats but not in male mice. There were no dose-related increases in tumor incidence in either sex in both species at exposures up to 75x and 224x for mice and rats at the recommended clinical administration based on AUC. Additional findings in the rat study were those associated with phospholipidosis at ≥ 200 mg/kg/day in males and at 600 mg/kg/day in females; and nephrotoxicity at 600 mg/kg/day.

5.5.4. Reproductive and Developmental Toxicology

Data (presented by FDA):

Fertility and Early Embryonic Development:

Study title/ number: Effects of TAK-385 on Fertility and Early Embryonic Development to Implantation in Rats /TAK-385/00113

Key Study Findings

- TAK-385 did not have adverse effects on fertility parameters, mating performance or embryonic findings on Day 15 of gestation

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing: 0, 40, 200 and 1000 mg/kg/day

Relugolix

Route of administration:	Oral gavage
Formulation/Vehicle:	Vehicle: 0.5% (w/v) methylcellulose solution
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	20/sex/group
Satellite groups:	none
Study design:	Rats were treated once daily -14 days before mating, through mating (≤ 3 weeks) and day before necropsy (Days 52-54; males) or Day 6 of gestation (females). Dams were euthanized on Day 15 of gestation. Non-mated females were also dosed until Day 41.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	HD: Defect of the incisor teeth in one male at Day 21 and another male at Day 46 of treatment. New incisor teeth were observed 9 or 11 days after defect was noted.
Body Weights	<u>Males</u> HD: Transient suppression of body weight gain (-52%) on Days 0 to 3 <u>Females</u> HD: Transient increase in body weight gain (41%) in dams on Days 10 – 13 of gestation
Food Consumption	<u>Males</u> Significant decrease (-24%) food consumption on Day 0 to 1 of treatment in HD males. However, there was statistically significant increase (up to 8%) in food consumption on Days 7 to 8 at \geq LD males. <u>Females</u> Before mating, HD females had significant decrease (up to -19%) in food consumption on Days 0 to 1 and 3 to 4 of treatment. In pregnant females, food consumption was 10% higher at HD on Days 0-1.
Estrous cycle	Unremarkable
Necropsy findings	No abnormalities were observed in gross pathology for any group, except for Male# 10052 at LD had small and soft testes and small epididymis
Fertility parameters: Mating/fertility index, corpora lutea, preimplantation loss, etc.	Unremarkable
Mating performance: Copulatory index, fertility index or mean copulatory interval	Unremarkable

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Embryonic findings: (Day 15 of gestation)	No significant differences were reported in number of live embryos, number of post-implantation losses, embryo viability or post-implantation loss rate
Toxicokinetics	Not conducted

LD: low dose; MD: mid dose; HD: high dose

-: indicates reduction in parameters compared to control.

Embryo-Fetal Development:

Study title/ number: Effects of TAK-385 on Embryo-Fetal Development in Rats /TAK-385/00110

Key Study Findings

- No significant treatment-related adverse effects reported

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing:

0, 40, 200, 1000 mg/kg/day, once daily from Day 6 to Day 17 of gestation

Route of administration:

Oral gavage

Formulation/Vehicle:

Vehicle: 0.5% (w/v) methylcellulose solution

Species/Strain:

Rat/Sprague-Dawley

Number/Sex/Group:

20 females/group

Satellite groups:

none

Study design:

Male and females were paired on a one-on-one basis for mating. 20 animals/group were confirmed to have copulated, which resulted in 19 to 20 pregnant females/group. Pregnant female rats of approximately 12 to 13 weeks of age received TAK-385 on GD 6-17. Animals were euthanized on GD 20.

Deviation from study protocol affecting interpretation of results:

No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	<u>Maternal</u> Body weight/Body gain MD: -4% GD 20/ -18% GD 18-20 HD: -4% GD 12-16, GD 20/ -21% GD 6-12 and -14% GD 18-20

Relugolix

	<u>Fetal (body weights)</u> Body weights were not affected by compound
Food Consumption	HD: up to -29% (GD 6-7), which reduced over time (-6%, GD 16-17)
Necropsy findings Cesarean Section Data	Pregnancy occurred in all rats, except for one female in control and one female in MD group. MD: 11.9% preimplantation loss (vs 4.5% control) No differences were reported in placental weight between control and treatment groups. Fused placenta was observed in 1 fetus each in LD and HD groups.
Necropsy findings Offspring	No visceral abnormalities were reported in any group. Mean frequency was higher in HD group vs controls for dilated ureter (3.61% HD vs 1.41% Ctrl) and convoluted ureter (2.89% HD vs 0% Ctrl) but frequencies were within the range of background data and not statistically significant. No skeletal abnormalities were observed in HD group. In control group, hemicentric thoracic centrum was noted. Cervical rib, asymmetry of sternebra, dumbbell-shaped thoracic centrum, splitting of thoracic centrum, wavy rib, short supernumerary rib or supernumerary lumbar vertebra were noted in both HD and/or control groups without any statistical significance.

LD: low dose; MD: mid dose; HD: high dose; GD: gestational day

-: indicates reduction in parameters compared to control.

Study title/ number: Effects of TAK-385 on Embryo-Fetal Development in Rabbits /TAK-385/00115

Key Study Findings

- TAK-385 at 9 mg/kg/day given to pregnant rabbits during period of organogenesis caused post-implantation losses, decrease in number of live fetuses and low fetal viability rate
- One fetus at 9 mg/kg/day had external malformations, i.e. meningoencephalocele and open eye, and another fetus had an absent claw. One fetus at 3 mg/kg/day had ectopia cordis with gastroschisis
- Visceral abnormalities were reported in one fetus in each treatment group at ≥ 1 mg/kg, and skeletal abnormalities were reported in one fetus at 3 mg/kg/day and two fetuses at 9 mg/kg/day

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Relugolix

Dose and frequency of dosing:	0, 0.3, 1, 3 and 9 mg/kg/day, once daily from Day 6 to Day 18 of gestation
Justification of doses:	Based on findings from a dose-ranging finding study in rabbits administered TAK-385 at doses up to 1000 mg/kg/day from Day 6 to Day 18 of gestation. Mortality occurred in all dams at 1000 mg/kg/day. Implants could not be confirmed in all females at ≥ 40 mg/kg/day and 2 females at 8 mg/kg/day. Post-implantation loss and decreased number of live fetuses were noted in pregnant females at 8 mg/kg/day. An increase in skeletal variations (full and short supernumerary ribs) was noted in fetuses at 8 mg/kg/day compared to control.
Route of administration:	Oral gavage
Formulation/Vehicle:	Vehicle: 0.5% (w/v) methylcellulose solution
Species/Strain:	Rabbit/Kbl:JW
Number/Sex/Group:	20 females/group
Satellite groups:	none
Study design:	Male and females were paired on a one-on-one basis for mating. 20 animals/group were confirmed to have copulated, which resulted in 17 to 20 pregnant females/group. Pregnant female rabbits, approximately 18 to 19 weeks of age, received TAK-385 on GD 6-18. Animals were euthanized on GD 28.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings																					
Mortality	There was no maternal mortality.																					
Clinical Signs	Control: External genital bleeding on GD 19 and 20, followed by abortion (GD 21) occurred in one dam (# 10005)																					
Body Weights	Maternal: Unremarkable Fetal: Unremarkable																					
Food Consumption	Unremarkable																					
Necropsy findings Cesarean Section Data	<p>Pregnancy occurred in all rats, except for one female in control and three females in 0.3 mg/kg/day group.</p> <p>Control: One rabbit aborted the litter on GD 21</p> <p>1 mg/kg/day: liver discoloration in 1/20 dams</p> <p>9 mg/kg/day: Complete litter loss reported in 7/20 dams</p> <table border="1" style="width: 100%; margin-top: 10px;"> <thead> <tr> <th colspan="2"></th> <th colspan="5">Litter data (mean)</th> </tr> <tr> <th>Dose mg/kg/day</th> <th></th> <th>0</th> <th>0.3</th> <th>1</th> <th>3</th> <th>9</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>			Litter data (mean)					Dose mg/kg/day		0	0.3	1	3	9							
		Litter data (mean)																				
Dose mg/kg/day		0	0.3	1	3	9																

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	Corpora lutea	9.6	9.4	10	9.5	9.5
	Implantation sites	8.8	8.0	8.7	8.1	8.4
	Live fetuses	7.9	7.3	7.9	8.0	4.7*
	Total fetuses	143	124	157	159	93
	Pre-implantation loss (%)	9.8	14.1	13.3	14.3	12.6
	Post-implantation loss (%)	9.4	7.8	8.4	2.5	43.9
	*p<0.05					
Necropsy findings Offspring	No significant differences were note in sex ratio.					
	Fetal external:					
		Dose mg/kg/day				
	Findings	0	0.3	1	3	9
	No. examined litter/fetus	18/143	17/124	20/157	20/159	13/93
	Meningoencephalocele					1/1 ^a
	Open eye					1/1 ^a
	Absent claw					1/1
	Gastroschisis				1/1 ^a	
	Ectopia cordis				1/1 ^a	
	a: occurred in same fetus					
	Fetal visceral:					
		Dose mg/kg/day				
	Findings	0	0.3	1	3	9
	No. examined litter/fetus	18/143	17/124	20/157	20/159	13/93
	Microphthalmia				1/1 ^a	
	Malpositioned subclavian branch	1/1				
	Retroesophageal subclavian			1/1	1/1 ^a	
	Narrowed pulmonary trunk				1/1 ^a	
	Right-sighted aortic arch				1/1 ^a	
	Ventricular septum defect				1/1 ^a	
	Persistent atrioventricular canal				1/1 ^a	
	Abnormal lung lobation					1/1 ^a
Abnormal liver lobation					1/1	
Small gallbladder					1/1 ^a	
Dilated cerebral ventricle				1/2		
a: occurred in same fetus						
Fetal skeletal:						
	Dose mg/kg/day					
Findings	0	3	9			
No. examined litter/fetus	18/143	20/159	13/93			
Fused sternebra			1/1			
Misaligned thoracic vertebra		1/1 ^a				
Fused lumbar arch		1/1 ^a				

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	Fused rib		1/1 ^a																															
	Absent rib		1/1 ^a																															
	Absent phalanx			1/1																														
	Cervical rib	3/3		1/1																														
	Asymmetry of sternebra	1/1	1/1																															
	Dumbbell-shaped thoracic centrum			1/1																														
	Splitting of thoracic centrum			1/1																														
	Short rib		1/1																															
Toxicokinetics	<table border="1"> <thead> <tr> <th>Gestational Day</th> <th>Dose (mg/kg)</th> <th>C_{max} (ng/mL)</th> <th>AUC₍₀₋₂₄₎ (ng·hr/mL)</th> </tr> </thead> <tbody> <tr> <td rowspan="4">6</td> <td>0.3</td> <td>0</td> <td>0</td> </tr> <tr> <td>1</td> <td>1.6</td> <td>2</td> </tr> <tr> <td>3</td> <td>5.5</td> <td>14</td> </tr> <tr> <td>9</td> <td>25.3</td> <td>56</td> </tr> <tr> <td rowspan="4">18</td> <td>0.3</td> <td>0.4</td> <td>0</td> </tr> <tr> <td>1</td> <td>3.6</td> <td>6</td> </tr> <tr> <td>3</td> <td>12.8</td> <td>25</td> </tr> <tr> <td>9</td> <td>53.3</td> <td>106</td> </tr> </tbody> </table> <p>Values are mean of n=3</p>				Gestational Day	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	6	0.3	0	0	1	1.6	2	3	5.5	14	9	25.3	56	18	0.3	0.4	0	1	3.6	6	3	12.8	25	9	53.3	106
	Gestational Day	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)																														
	6	0.3	0	0																														
		1	1.6	2																														
		3	5.5	14																														
		9	25.3	56																														
	18	0.3	0.4	0																														
		1	3.6	6																														
		3	12.8	25																														
		9	53.3	106																														

GD: gestational day

The Applicant's Position:

In the rat, relugolix had no effect on fertility or early embryonic development (TAK-385/00008), was not teratogenic, and had no effect on the estrous cycle at oral doses up to 1000 mg/kg/day. In the rabbit, relugolix caused embryofetal death, but did not cause fetal malformations, at oral doses of 9 mg/kg/day. The NOAEL for embryofetal development in rabbits was 3 mg/kg/day (AUC₀₋₂₄ = 25 ng·hr/mL). In a pre- and postnatal toxicity study in pregnant rats administered relugolix at doses up to 1000 mg/kg/day from gestational day 6 through postnatal day 20 (TAK-385/00007 and TAK-385/00110), there were no adverse effects on first generation (F1) animals' estrous cycle, copulation index, copulatory interval, fertility index, the number of corpora lutea, the number of implantation sites, implantation rate, or necropsy findings. There were also no adverse effects on second generation (F2) embryo number of pre-implantation losses, pre-implantation loss rate, the number of post-implantation losses, post-implantation loss rate, or the number of live embryos. The NOAEL for F0 dams, development in F1 pups/animals, reproductive function in F1 animals, and early embryonic development of F2 embryos was 1000 mg/kg/day.

In male GnRH receptor knock-in mice, relugolix induced a dose-dependent decrease in prostate and seminal vesicle weights at 3 to 10 mg/kg twice daily. The suppressive effects of relugolix were reversible, with the exception of testes weight, which did not

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recover within 28 days after drug withdrawal (Nakata et al. 2014). However, there were no treatment-related effects on testes weight in male monkeys at relugolix doses up to 50 mg/kg/day in the 39-week repeat-dose study.

The FDA's Assessment:

Reproductive and developmental toxicology studies were reviewed under (b) (4). FDA agrees with the Applicant's summary of rat findings of relugolix on fertility, mating and embryo-fetal development findings. These studies were not needed given the prostate cancer indication and expected adverse effects on these parameters based on its mechanism of action. The limited findings in rat studies is not surprising given the low binding affinity of relugolix to rat GnRH receptors and thus, may not be relevant and/or misleading to appropriately inform reproductive and developmental toxicology. While relugolix (TAK-385) had no adverse effects on fertility in the rat study and repeat-dose general toxicology studies in monkeys did not demonstrate TAK-385-related effects on male reproductive organs, relugolix is expected to impair fertility based on primary pharmacology findings. A single administration study shows that TAK-385 at ≥ 1 mg/kg reduced plasma levels of luteinizing hormone (see Primary Pharmacology) in castrated monkeys. Additionally, findings with human GnRH receptor knock-in male mice show that oral administration of TAK-385 for 28 days decreased prostate and testes organ weight similar to castrate levels and reduces serum testosterone levels. Recovery of testosterone levels was noted but graphed results showed variability and recovery of prostate weight but not testes were observed after discontinuation of TAK-385.

The Applicant did not submit data on binding affinity to rabbit GnRH receptor. In the rabbit study (Study# TAK-385/00115), embryo-fetal deaths were noted at 9 mg/kg/day. We note fetal malformations, abnormalities or variations occurred in one or 2 fetuses with doses tested; however, given the low incidence or in some cases occurred in controls, the fetal malformations, abnormalities or variation findings are most likely spontaneous. No significant differences were noted in skeletal variations frequencies or number of ossified sacral and caudal vertebrae between control and 3 and 9 mg/kg/day groups.

The pre- and post-natal study conducted in rats (Study# TAK-385-300136) was not reviewed at this time based on a prostate cancer indication and may not be relevant due to the low binding affinity.

5.5.5. Other Toxicology Studies

The Applicant's Position:

Antigenicity: No antigenicity studies have been conducted for relugolix.

Immunotoxicity: No immunotoxicity studies have been conducted for relugolix. There is no cause for concern for immunotoxicity potential based on the intended patient population, mechanism of action, and non-peptide structure of relugolix. Furthermore, there were no findings suggestive of effects on the immune system in general toxicity studies conducted in mice for up to 13 weeks, rats for up to 26 weeks, or monkeys for up to 39 weeks.

Mechanistic: The sensitivity of urinary di-docosahexaenoyl (22:6)-bis(monoacylglycerol) phosphate (di-22:6-BMP) as a biomarker for PLD was evaluated after oral administration of relugolix to male Sprague-Dawley rats at doses of 0 (control), 30, or 1000 mg/kg for 28 days (TAK-385/13010). At 1000 mg/kg/day, light microscopy (mild foamy cell infiltrates in the lungs/lymph nodes), transmission electron microscopy (prominent multilamellar cytoplasmic bodies in lymphocytes), and di-22:6-BMP biomarker analysis (2- to 3-fold increase in urine, lungs, and testes relative to control animals) demonstrated treatment-related changes indicative of PLD. Based on this study, urinary di-22:6-BMP is a potential biomarker for detection of PLD in rats exposed to relugolix.

Dependence: No dependence studies have been conducted for relugolix. Relugolix did not bind to any targets associated with neuronal systems related to abuse potential (eg, dopamine, serotonin, gamma-aminobutyric acid, opioid, cannabinoid, N-methyl-D-aspartate, ion-channel complexes, transporters). Relugolix is a substrate of the efflux transporter P-gp, and in rats there is very low exposure to relugolix-related radioactivity in the CNS following an oral dose of [¹⁴C]-relugolix. Based on these data, there is no concern about drug dependence.

Metabolites: There were no observed major circulating human metabolites, and biotransformation pathways for relugolix are similar between the nonclinical species and humans. Metabolites are considered to have been qualified in the course of routine nonclinical testing and no additional studies with relugolix metabolites were considered necessary for this program.

Impurities: Qualification of relugolix impurities in routine Good Laboratory Practice (GLP) nonclinical toxicology studies supports human daily intakes associated with drug substance and drug product specification limits in accordance with International Council for Harmonisation (ICH) Q3A(R2), ICH Q3B(R2), or ICH M7(R1). Qualification of relugolix impurities in routine GLP nonclinical toxicology studies supports human daily intakes associated with specification limits.

(b) (4), an impurity and degradation product in the drug substance, was shown to be mutagenic in bacteria in the presence of rat S9 fractions (TAK-385/10011). Results of additional in vitro genotoxicity studies in mammalian cells and in vivo studies in rodents with this impurity were negative (TAK-385/10075, TAK-385/10093, TAK-385/10081, or TAK-385/10082) enabling determination of a permissible daily exposure limit and is considered fully qualified.

Phototoxicity: Relugolix absorbs ultraviolet light and based on this absorption characteristic in vitro and in vivo studies of relugolix were performed. Relugolix elicited a phototoxic response in an in vitro 3T3 Neutral Red Uptake phototoxicity study (TAK-385/00013). Therefore, an in vivo phototoxicity study of relugolix was conducted in male hairless mice. Mice were administered a single dose of relugolix at doses of 0 (control), 200, 600, or 2000 mg/kg by oral gavage followed by exposure to simulated sunlight (ultraviolet radiation) (TAK-385/00112). Irradiation of a circular patch of skin was conducted at a 0.5 minimal erythema dose level. No skin reactions indicative of phototoxicity were observed in any of the rats administered the control or relugolix up to 2000 mg/kg followed by a single exposure to ultraviolet radiation.

The FDA's Assessment:

The FDA generally agrees with the Applicant's comments and conclusions on antigenicity, immunotoxicity, dependence, metabolites, impurities and phototoxicity. The in vivo phototoxicity study and in silico, in vitro and in vivo genotoxicity studies evaluating impurities were reviewed under (b) (4). The mechanistic studies to evaluate a biomarker for phospholipidosis were not reviewed or necessary to support approval of this application.

The CMC drug product and substance reviewers requested qualification levels of impurities (b) (4). The proposed criteria in the drug substance or drug product are (b) (4). Impurities (b) (4) were qualified by the general toxicology studies conducted in rats, with safety margins ranging from (b) (4) at the clinical loading dose of 360 mg. The toxicology batch of the 2-year carcinogenicity study contained a higher level of (b) (4) (%) compared to repeat-dose studies ((b) (4) %), which provided a safety margin of (b) (4) at 360 mg.

According to ICH S9 Question and Answers guidance, genotoxicity assessment of impurities should be conducted if the active pharmaceutical ingredient is not genotoxic and the impurity exceeds the ICH Q3A/B qualification threshold. At the maximum dose of 360 mg relugolix, the proposed criteria exceed the qualification thresholds of ICH Q3B(R2) for impurities. In silico assessments (MCASE and DEREK) did not identify structural alerts for genotoxicity for impurities (b) (4), but based on its (b) (4) (b) (4) moiety, (b) (4) showed mutagenic potential. (b) (4) was also mutagenic in the bacterial reverse mutation assay in strain TA98 with metabolic activation with rat S9 but was negative in subsequent in vitro and in vivo genotoxicity assays, including a rat micronucleus test and a transgenic rodent mutation model, Muta™ Mice, that evaluated gene mutations in the lacZ transgene in liver and bone marrow of mice after 28-day repeat-dosing with (b) (4) impurity. These studies were fully reviewed under (b) (4) (b) (4). Based on the totality of data, FDA concluded that (b) (4) did not pose a genotoxic risk for human subjects when present at levels up to 1.25 mg/day. For the prostate cancer indication, the expected maximum human dose administered with relugolix is the loading dose at 360 mg on the first day, which is then followed by 120 mg/day. At the proposed specification of (b) (4) %, the exposure at the loading dose is (b) (4) and

Relugolix

(b) (4) mg for continued maintenance. Compared to the permitted daily exposure (1.25 mg/day), the safety margin of exposure for (b) (4) at the 360 mg and 120 mg doses, respectively. As previously mentioned, in the 2-year carcinogenicity studies in rats, where relugolix (b) (4) impurity levels were at (b) (4) % providing a (b) (4) safety margin based on AUC at the human maximum loading dose, relugolix did not induce tumors. In conclusion, Impurities (b) (4) are qualified based on the toxicology studies conducted in rats and levels in the drug substance and product are acceptable. Based on the available information from the genotoxicity assessments for impurity (b) (4), the proposed advanced cancer indication, the carcinogenicity study results with relugolix and that the loading dose will only be administered on the first day of therapy, there are no pharmacology/toxicology concerns for impurity (b) (4).

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Claudia Miller

Tiffany Ricks

Primary Reviewer

Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA’s Assessment:

Relugolix is a gonadotropin releasing hormone (GnRH) receptor antagonist indicated for the treatment of patients with advanced prostate cancer. The proposed dosage regimen is a single loading dose of 360 mg (120 mg × 3 tablets) orally followed by 120 mg taken once daily (QD) with or without food.

The evidence of safety and efficacy was supported by a phase 3, randomized, open-label, parallel-group study in men with androgen-sensitive advanced prostate cancer who required at least 1 year of continuous ADT (MVT-601-3201). Patients were randomized (2:1) to relugolix arm (N=624), or leuprolide arm (N=310). The lower bound of the 95% CI of the sustained castration rate (< 50 ng/dL) was 94.9% (> 90%). Relugolix was generally well tolerated and consistent with class effects of other GnRH agonists. The clinical pharmacology review focused on the dose selection, dose recommendations in patients with organ dysfunctions, and the assessment of drug-drug interaction potential of relugolix.

The proposed dosage regimen of relugolix is acceptable based on the efficacy and safety results demonstrated in the Phase 3 trial. Dose adjustment is not needed for patients with mild to moderate hepatic impairment, or patients with mild to severe renal impairment. Co-administration of relugolix with P-gp inhibitors should be avoided, as co-administration with erythromycin (a P-gp inhibitor) increased the AUC and C_{max} of relugolix by 6.2-fold, which may increase the risk of relugolix adverse reactions. If co-administration is unavoidable, take the P-gp inhibitor at least 6 hours after relugolix and monitor patients more frequently for adverse reactions. Treatment with relugolix may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors (e.g., macrolide antibiotics). If treatment with relugolix is interrupted for more than 7 days, resume relugolix with a 360 mg loading dose on the first day followed by 120 mg once daily.

Co-administration of relugolix with combined P-gp and strong CYP3A inducers should be avoided, as co-administration with rifampin (a combined P-gp and strong CYP3A inducer) decreased the AUC of relugolix by 55%, which may reduce relugolix activity. If co-coadministration is unavoidable, increase the relugolix maintenance dose to 240 mg QD.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 214621 and recommends approvable. The key review issues with the specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
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Relugolix

<p>Pivotal and Supportive evidence of effectiveness</p>	<p>The primary evidence of effectiveness comes from a phase 3 Study MVT-601-3201, which demonstrated that 96.7% (95% CI: 94.9%, 97.9%) of patients who received relugolix maintained continuous testosterone suppression below castrate levels (< 50 ng/dL) for 48 weeks from Day 29 to Day 337.</p>
<p>General dosing instructions</p>	<p>The proposed dosage regimen for relugolix:</p> <ul style="list-style-type: none"> • Initiate treatment of relugolix with a loading dose of 360 mg on the first day and continue treatment with a 120 mg dose taken orally once daily with or without food at approximately the same time each day. Instruct patients to swallow tablets whole and not to crush or chew tablets. • Advise patients to take a missed dose of relugolix as soon as they remember. If the dose was missed by more than 12 hours, patients should not take the missed dose and resume with the next scheduled dose. • If treatment with relugolix is interrupted for greater than 7 days, restart relugolix with a loading dose of 360 mg on the first day and continue with a dose of 120 mg once daily. <p style="text-align: right;">(b) (4)</p> <p>In conclusion, the proposed relugolix dose of a single loading dose of 360 mg orally followed by 120 mg QD is acceptable from a clinical pharmacology perspective.</p>

Relugolix

(b) (4)		(b) (4)
Drug-drug interactions	<ul style="list-style-type: none"> • (b) (4) Co-administration of relugolix with a P-gp inhibitor increased the AUC and C_{max} of relugolix by 6.2-fold, which may increase the risk of relugolix adverse reactions. If co-administration is unavoidable, take the P-gp inhibitor at least 6 hours after relugolix and monitor patients more frequently for adverse reactions. Treatment with relugolix may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors (b) (4). If treatment with relugolix is interrupted for more than 7 days, resume relugolix with a 360 mg loading dose on the first day followed by 120 mg once daily. • (b) (4) Co-administration relugolix (b) (4) (a combined P-gp and strong CYP3A inducer) decreased the AUC and C_{max} of relugolix (b) (4) 	
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.	

Post-Marketing Requirements and Commitments

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMC	Alternative dosing strategy when co-administration of relugolix with P-gp	Observed pharmacokinetic data using the dose separation strategy	Conduct a pharmacokinetic study to evaluate the effect of P-gp inhibitors when administered after relugolix to further inform dosing strategy. Submit the

Relugolix

	inhibitors is unavoidable.	are needed to further inform product labeling.	datasets with the final study report. The study results may inform product labeling.
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6.2. Summary of Clinical Pharmacology Assessment

The Applicant's Position:

The clinical pharmacology program for relugolix includes a total of 13 studies: one biopharmaceutics study and 12 dedicated clinical pharmacology studies that provide assessments of the pharmacokinetics, pharmacodynamics, and safety and tolerability of relugolix after administration of single doses ranging from 20 to 360 mg and multiple doses ranging from 40 to 180 mg. Studies included a human ADME and absolute bioavailability study, three studies for special populations (moderate renal impairment, severe renal impairment, and mild and moderate hepatic impairment), 6 drug interaction studies, and a thorough QT/QTc study, which supported both the prostate cancer (360-mg loading dose, followed by 120-mg once daily) [REDACTED] (b) (4) [REDACTED]. The pharmacokinetics of relugolix have been appropriately characterized, exposure data provided reference human exposures for nonclinical safety margins and the pharmacodynamic data informed dose selection. Drug interaction studies identified clinically meaningful effects of other drugs on the exposure to relugolix (victim interactions) and, along with in vitro data, ruled out important effects of relugolix on other drugs (perpetrator interactions) to guide dosing recommendations for concomitant use. Additionally, data from five phase 1, phase 2, and phase 3 studies combined were used to develop a population pharmacokinetic (PopPK) model to assess the effect of intrinsic factors (demographic parameters [age, race, and body size {body mass index and body weight}] and renal function [mild to severe renal impairment]) on the pharmacokinetics and/or exposure to relugolix and a semi-mechanistic PopPK/pharmacodynamic (PD) model to characterize the exposure-response profile of relugolix using relugolix and testosterone concentration data. Simulations using the PopPK/PD model were used to assess the impact of covariates on testosterone concentrations and to define clinically meaningful decreases in relugolix exposure or the lower boundary of acceptance criteria to facilitate interpretation from dedicated studies and covariate analyses.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

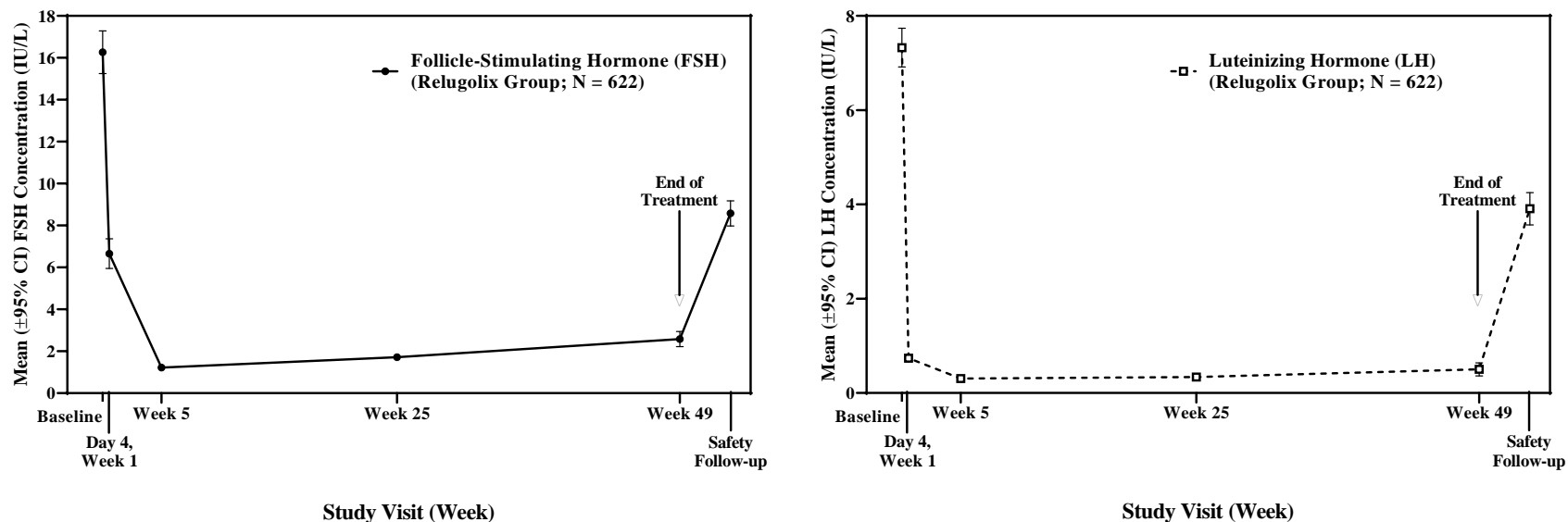
Mechanism of Action and Pharmacodynamics

Relugolix is an orally active, non-peptide GnRH receptor antagonist that competitively binds to GnRH receptors on gonadotrophic neurons, blocking endogenous GnRH from binding to and subsequent activation of GnRH receptors, preventing the release of LH and FSH from the anterior pituitary gland. As a result, circulating concentrations of LH

and FSH are considerably reduced, resulting in decreased testosterone production by Leydig cells of the testes and a subsequent marked decrease in systemic testosterone concentrations. After administration of a 360-mg single dose of relugolix in healthy men (C27001 Part 1), mean serum LH and FSH concentrations rapidly declined (within 2 hours postdose) with LH concentrations decreased to a nadir by 24 hours postdose and FSH concentrations decreased throughout the 48-hour sampling period. Mean serum testosterone concentrations also rapidly declined (within 4 hours postdose), reaching a nadir at 36 hours postdose with castrate levels (testosterone < 50 ng/dL) achieved by mean (range) 16 (12 to 24) hours postdose, supporting a 360-mg dose as a loading dose to achieve rapid reduction of testosterone concentrations to castrate levels. Upon multiple-dose administration of 120-mg doses once daily, testosterone concentrations were consistently maintained at castrate levels during treatment (C27001 Part 2 and Part 3).

In the pivotal phase 3 study in men with advanced prostate cancer (MVT-601-3201), relugolix 120 mg once daily, following a single oral loading dose of relugolix 360 mg on Day 1, was associated with rapid reductions in LH and FSH concentrations that remained consistently low during treatment (see [Figure 1](#)). Correspondingly, testosterone concentrations were suppressed within 4 days and were maintained through 48 weeks of treatment with relugolix (see [Figure 11](#)).

Figure 1: Follicle-Stimulating Hormone and Luteinizing Hormone Concentrations over Time (Mean ± 95% CI) (Study MVT-601-3201)



Abbreviations: CI = confidence interval; FSH = follicle-stimulating hormone; LH = luteinizing hormone; N = number.
Source: Figure 23, Module 2.7.2.

Pharmacokinetic Properties

After oral administration, relugolix is rapidly absorbed, with an absorption profile associated with multiple postdose absorption peaks. After reaching C_{max} , relugolix declines in a multiphasic manner, initially rapidly, followed by a slower decline and subsequently by a slow (relatively flat) terminal elimination phase; the half-life associated with this portion of the concentration-time profile is approximately 60.8 hours. However, this portion of the concentration-time profile is associated with low concentrations of relugolix and does not significantly contribute to the overall exposure. An effective half-life, or the half-life responsible for the approximately 2-fold accumulation during once daily administration, is approximately 25 hours. Following a loading dose of 360 mg, steady-state is reached after 7 days of once daily administration with 120-mg doses. Relugolix C_{max} and area under the concentration-time curve (AUC) increased in proportion or greater than in proportion to dose after administration of single doses ranging from 60 to 360 mg and multiple doses ranging from 20 to 180 mg once daily.

ADME Properties

Absorption: Relugolix is a sensitive P-gp substrate and intestinal P-gp efflux is the primary determinant of relugolix absorption and oral bioavailability. The mean absolute bioavailability of relugolix is 11.6%. After oral administration, relugolix is rapidly absorbed, with an initial absorption peak observed by 0.5 hours postdose, followed by one or more subsequent absorption peaks, any of which may represent the C_{max} . The median time to C_{max} (t_{max}) is 2.25 hours. Although consumption of a high-calorie, high-fat meal is associated with a decrease in the exposure to relugolix, the effect (average 20% reduction) is not considered clinically meaningful and therefore, relugolix may be taken with or without food.

Distribution: In the human ADME and absolute bioavailability study (TAK-385-1009), lower concentrations of radioactivity were observed in whole blood compared with plasma (mean whole blood-to-plasma ratio of 0.78), indicating limited distribution into red blood cells. In vitro data showed that relugolix is 68.2% to 70.8% bound to plasma proteins, primarily to albumin. The volume of distribution of relugolix is high in humans based on estimates of V_c/F (7053 L), V_p1/F (11,730 L), and V_p2/F (14,550 L) from the PopPK model. Results of in vitro transporter studies in OATP-expressing cells indicated that relugolix is not a substrate for the OATP1B1 or OATP1B3 hepatic uptake transporters.

Metabolism: Relugolix is metabolized through multiple pathways, including CYP3A and CYP2C8 (minor pathways) and other minor unidentified pathways. In addition, unabsorbed drug is metabolized by intestinal microflora. After administration of a single 80-mg (127 μ Ci [4.7 MBq]) dose of [14 C]-relugolix in the human ADME and absolute bioavailability study (TAK-385-1009), relugolix was the primary drug-related component in plasma (up to 68.2% of total radioactivity in plasma). There are no major

Relugolix

metabolites of relugolix. All identified relugolix metabolites were formed in nonclinical toxicology species. Additionally, several minor, unidentified, polar relugolix metabolites were observed in rat and monkey excreta (and rat bile) with corresponding metabolites observed in human urine and feces based on a comparison of chromatographic profiles.

Excretion: After oral administration of a single 80-mg (127 μ Ci [4.7 MBq]) dose of [14 C]-relugolix in the human ADME study (TAK-385-1009), approximately 4.1% and 80.6% of the administered dose was excreted in the urine and feces, respectively. Relugolix-derived radioactivity was excreted primarily as metabolites, where unchanged drug accounted for only 6.4% of the administered dose in excreta (2.2% in urine and 4.2% in feces).

Elimination: Based on collective data from human and nonclinical ADME studies, multiple elimination pathways contribute to the systemic clearance of relugolix. Metabolism is the primary route of elimination through multiple biotransformation pathways, including CYP3A and CYP2C8 (minor pathways) and other minor unidentified pathways. Renal excretion of unchanged drug into the urine accounts for approximately 19% of systemic clearance. Biliary secretion of unchanged drug may also contribute to relugolix elimination. Total clearance following intravenous dosing was 29.4 L/hr. The mean terminal phase half-life is 60.8 hours and the effective half-life was 25 hours.

The Applicant's Position:

The clinical pharmacology program provided data to characterize the pharmacokinetic and pharmacodynamic profile of relugolix. Biologic evidence of the mechanism of action of relugolix as a GnRH receptor antagonist ie, suppression of pituitary and testicular hormones, including the time-course of effects and dose-dependency are well-characterized in clinical studies and support dosing recommendations. The pharmacokinetics of relugolix is characterized by rapid absorption after oral administration, followed by multiple post-dose absorption peaks and thereafter, a multiphasic decline. The rapid absorption of relugolix is consistent with the rapid onset of action with decreases in testosterone concentrations occurring within hours postdose. The terminal elimination half-life of 60.8 hours reflects the relatively slow terminal elimination profile, although this portion of concentration-time profile does not significantly contribute to the total exposure (AUC). A 2-fold accumulation is observed upon once-daily administration, with an effective half-life of 25 hours, supporting once daily administration. Steady-state is achieved within 7 days when a loading dose of relugolix is administered. Relugolix is a substrate for intestinal P-gp, which is thought to limit its oral bioavailability (absolute bioavailability of 11.6%), be responsible for clinically meaningful drug interactions, and govern absorption-mediated increases in exposure in patients with moderate and severe renal impairment. The greater than proportional increases with respect to dose observed in some studies is thought to be due to saturation of intestinal P-gp. Metabolism, by multiple minor pathways, is the primary route of elimination, with renal excretion of unchanged drug

contributing to approximately 19% of systemic clearance. Biliary secretion of unchanged drug is a minor elimination pathway of systemic clearance.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Regarding the dose proportionality assessment, FDA clarifies that the AUC_{0-inf} and C_{max} of relugolix increases approximately dose proportionally over a single dosage range from 60 mg to 360 mg. Following multiple dosages of relugolix from 20 mg to 180 mg once daily, AUC_{tau} increases approximately dose proportionally and C_{max} increases greater than dose proportionally. FDA clarifies that of the 11.6% absorbed dose, up to 68.2% of the radioactivity detected in plasma belongs to the parent drug (relugolix) and the remaining belongs to multiple metabolites.

6.2.2. General Dosing and Therapeutic Individualization

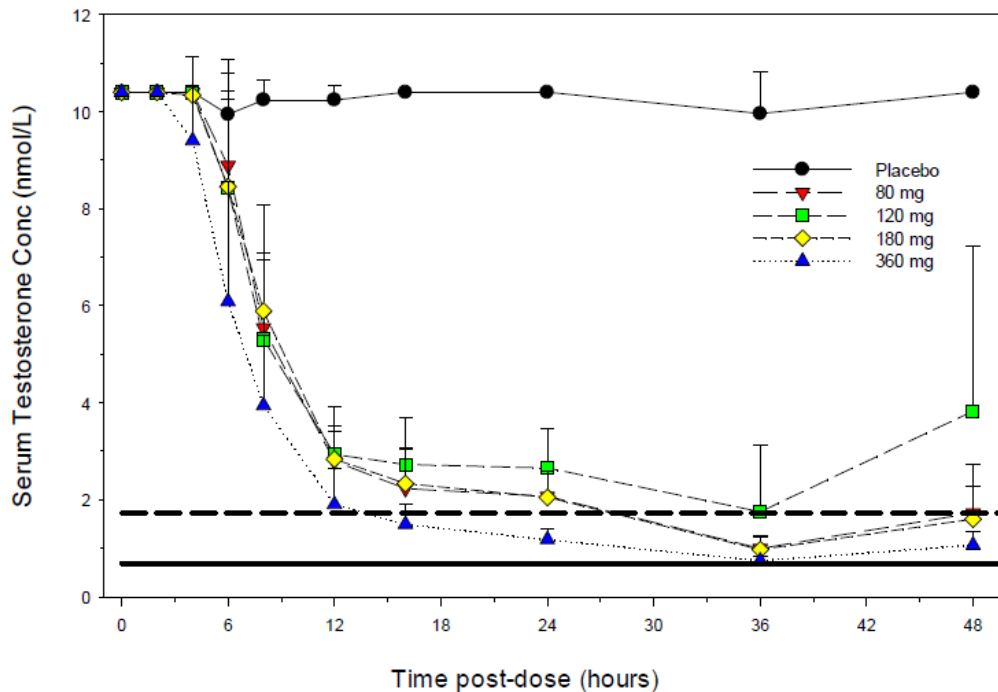
6.2.2.1. General Dosing

Data:

Dose Selection

In the safety, tolerability, pharmacokinetics and pharmacodynamics study in healthy men (C27001), after administration of a single 360-mg dose of relugolix, the initial decrease in testosterone concentrations occurred more rapidly than with lower doses (ranging from 80 to 180 mg) with mean testosterone concentrations that approximated 50 ng/dL by 16 hours postdose and remained < 50 ng/dL through 24 hours postdose (see [Figure 2](#)). The rapid reduction in testosterone to therapeutic concentrations after administration of a single 360-mg dose of relugolix suggested that this dose could be considered as a loading dose in order to achieve castrate levels of testosterone within the first day of the initiation of treatment.

Figure 2: Mean (SD) Time-Course of Serum Testosterone Suppression Following Single Dose Administration of Relugolix (Study C27001 Part 1)



Abbreviations: Conc = concentration; SD = standard deviation.

Note: Dotted and solid lines represent testosterone concentrations < 1.73 nmol/L (< 50 ng/dL; castrate levels) and < 0.69 nmol/L (< 20 ng/dL; profound castrate levels), respectively.

Source: Figure 1, Module 2.7.2.

Also in the safety, tolerability, pharmacokinetics and pharmacodynamics study in healthy men (C27001), after achieving testosterone concentrations < 50 ng/dL with once daily administration of 80-, 160- or 180-mg doses without a loading dose, testosterone concentrations were more consistently maintained, with a lower degree of variability, compared with lower doses with or without a loading dose, indicating that testosterone would be more constantly suppressed with daily doses between 80 and 180 mg.

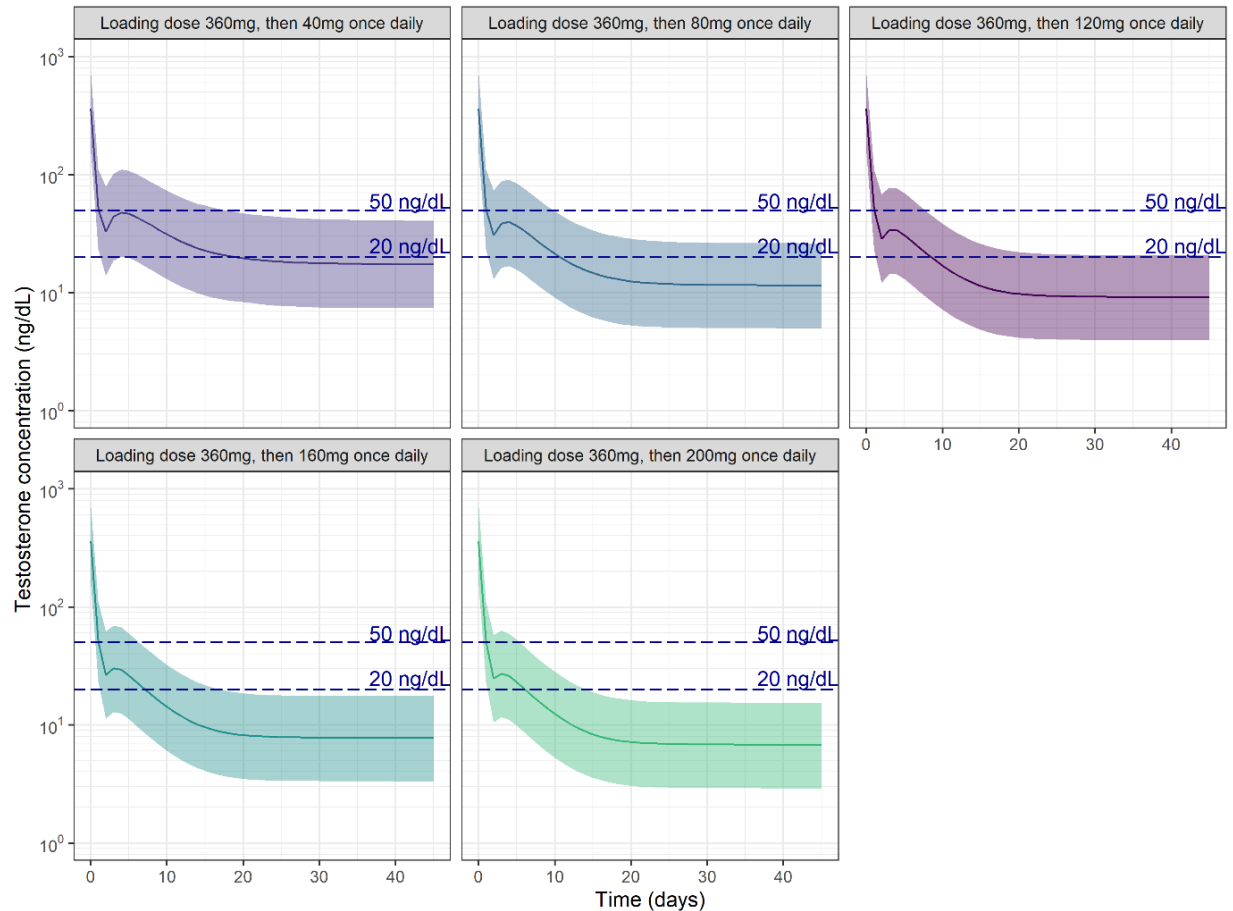
Upon administration of lower doses of relugolix (eg, 20 mg) once daily for 14 days following loading dose regimens of 320 mg/160 mg (Day 1/Day 2) or 320/240/160 mg (Day 1/Day 2/Day 3), the initial reductions in testosterone concentrations achieved with the loading doses were not maintained thereafter with mean testosterone concentrations becoming above 50 ng/dL by approximately 3 to 4 days after initiation of study treatment, indicating that the daily dose is important for maintaining testosterone concentrations within the target range over time. These data suggest that loading doses on days subsequent to the first day do not necessarily provide additional therapeutic benefit and that the dose for the daily dosing regimen is important for maintaining testosterone concentrations within the target range over time.

NDA/BLA Multi-disciplinary Review and Evaluation: NDA 214, 621
Relugolix

A 320-mg loading dose followed by 80- or 120-mg doses once daily was evaluated in phase 2 studies, but because a 360-mg dose provided a similar rapid reduction in testosterone concentrations and the dose can be more conveniently administered as 3 × 120 mg tablets, the dose and tablet strength used for daily administration, the 360-mg dose was selected as the loading dose for further evaluation in phase 3 studies.

Data from 899 participants (from phase 1, 2, and 3 studies) with both relugolix and testosterone concentration data were combined for PopPK and PopPK/PD analyses. Simulations using the final PopPK/PD model show that administration of a 120-mg dose of relugolix once daily following a single loading dose of 360 mg on Day 1 is associated with testosterone concentrations that decline more quickly with ≥ 90% of patients are predicted to maintain testosterone at profound castrate levels of testosterone (< 20 ng/mL), proportionally compared with lower doses (see [Figure 3](#)). Simulations also demonstrated that higher relugolix doses are unlikely to be more efficacious.

Figure 3: Simulated Testosterone Concentrations for Various Relugolix Once Daily Doses, Following a Single Loading Dose of Relugolix 360 mg



Notes: Relugolix was administered for 45 days to demonstrate time to reach threshold testosterone concentrations after which testosterone concentrations remain suppressed. Testosterone concentrations of < 50 ng/dL, and < 20 ng/dL represent castrate levels and profound castrate levels.

The shaded area represents the 90% prediction interval of the simulations. The solid lines represent the median of the simulations.

Source: Figure 28, MYOV-PMX-RELUGOLIX-1816 Report 1.

Food Effects

The AUC and C_{max} of relugolix is decreased by approximately 20% following consumption of a high-calorie, high-fat meal (geometric mean ratio [GMR] [fed/fasted] and 90% CI for the area under the concentration-time curve from time zero extrapolated to infinity [$AUC_{0-\infty}$] and C_{max} were 0.8116 [0.6436, 1.0234] and 0.7859 [0.5288, 1.1679], respectively).

Dosing Interval

Upon once daily administration, relugolix is associated with an approximately 2-fold accumulation, which corresponds to an calculated effective half-life of 25 hours (see Section 6.2.1).

The Applicant's Position:

The recommended dosing regimen of relugolix for the treatment of advanced prostate cancer is a single loading dose of 360 mg (three 120-mg tablets) on the first day followed by 120 mg taken once daily, at approximately the same time each day. The dosing recommendation for relugolix is supported by pharmacodynamic data, initially from clinical pharmacology studies, demonstrating rapid (within hours), dose-dependent (with respect to degree and duration) reductions in testosterone concentrations. After administration of a 360-mg dose, testosterone concentrations reach castrate levels within the first 24 hours, highlighting the importance of a loading dose. The daily dose of 120 mg is supported by pharmacodynamic data that showed that reductions in testosterone concentrations were more consistently maintained and with a lower degree of variability at doses greater than 80 mg, with the 120-mg dose maintaining testosterone at castrate levels. Simulations of testosterone concentrations using a semi-mechanistic and predictive exposure-response (PopPK/PD) model, showed that the 120-mg daily dose is the minimum maximally effective dose of relugolix.

Relugolix may be taken with or without food. Although a 20% reduction in the exposure to relugolix was observed with a high-calorie, high-fat meal, PopPK/PD model-based simulations predicted that even with a 50% reduction in relugolix exposure, $\geq 90\%$ of patients will achieve and maintain testosterone concentrations at castrate levels (< 50 ng/dL), demonstrating that efficacy is maintained even with modest decreases in exposure to relugolix.

Based on the 2-fold accumulation associated with relugolix after once daily administration of relugolix, an effective half-life of 25 hours was determined, supporting once-daily administration.

The FDA's Assessment:

FDA agrees with Applicant's proposed dosage regimen of a single loading dose of 360 mg on the first day followed by 120 mg taken once daily (QD) based on the following rationales:

1. A single loading dose on the first day (320 mg or 360 mg) reduced testosterone levels to castrate level (< 50 ng/dL) within 24 hours post-dose. The 360 mg loading dose was selected because it can be accomplished by taking three 120 mg tablets.
2. A daily maintenance dose of at least 80 mg QD is required to maintain castrate levels over time.

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3. The daily dose of 120 mg achieved slightly higher profound castration rate (< 20 ng/dL) with a lower degree of variability compared to the daily dose of 80 mg.
4. PopPK/PD modeling and simulation supported the proposed dosage regimen, which lead to rapid reduction of testosterone levels with $\geq 90\%$ of patients are predicted to maintain profound castrate levels (< 20 ng/dL). Higher relugolix once daily maintenance doses (e.g. 160 mg or 200 mg QD) are unlikely to be more efficacious. Additionally, a 50% decrease in exposure of relugolix is unlikely to have a significant effect on efficacy with respect to percentage of patients achieving castrate levels (< 50 ng/dL).

FDA agrees that relugolix may be taken with or without food since a high-calorie, high-fat meal reduced the AUC and C_{max} of relugolix by 19% and 21%, respectively, which is not considered clinically meaningful.

6.2.2.2. Therapeutic Individualization

Data:

Specific Populations

Age, Race, and Body Weight: Results from the PopPK analysis did not identify clinically meaningful differences of age, race, or body weight on the exposure to relugolix (post-hoc steady-state AUC [AUC_{ss}] or trough concentrations [$C_{trough,ss}$]). Post-hoc median AUC_{ss} and $C_{trough,ss}$ for the Black/African American race was 42% and 35% higher, respectively, compared with non-Black/African American race, although in a simulated population of 10,000 individuals (sampled, with replacement from the phase 3 study population), median AUC_{ss} and $C_{trough,ss}$ estimates were only 26% and 16% higher, respectively, indicating that the impact of Black/African American race on the exposure to relugolix in a broader population would be relatively modest and not considered to be clinically meaningful. Importantly, simulations using the PopPK/PD model showed no differences in median and 90% CI testosterone concentrations with respect to age, race, or body weight.

Patients with Hepatic Impairment: In patients with mild hepatic impairment (Class A, as determined by the Child-Pugh classification system) (MVT-601-1002), the $AUC_{0-\infty}$ and C_{max} of relugolix were decreased by 31% and 24%, respectively, compared with healthy participants with normal hepatic function (GMR [mild hepatic impairment/normal hepatic function] and 90% CI for the $AUC_{0-\infty}$ and C_{max} of relugolix were 0.6860 [0.3543, 1.3282] and 0.7567 [0.2958, 1.9357], respectively). In patients with moderate hepatic impairment (Child-Pugh Class B), the $AUC_{0-\infty}$ was decreased by 5% whereas the C_{max} was increased by 1.17-fold compared with healthy demographically matched participants with normal hepatic function (GMR [moderate hepatic impairment/normal hepatic function] and 90% CI for the $AUC_{0-\infty}$ and C_{max} of relugolix were 0.9451 [0.4581, 1.9500] and 1.1736 [0.4162, 3.3093], respectively). The influence of severe hepatic impairment on the pharmacokinetics of relugolix has not been evaluated.

Patients with Renal Impairment: After administration of a single 40-mg dose of relugolix to patients with moderate renal impairment (creatinine clearance [CL_{cr}] 30 to 59 mL/min, as estimated by the Cockcroft Gault equation), the exposure AUC_{0-∞} and C_{max} of relugolix were both increased by 1.5-fold compared with healthy control subjects with normal renal function (CL_{cr} ≥ 90 mL/min) (GMR [moderate renal impairment/normal renal function] and 90% CI for the AUC_{0-∞} and C_{max} of relugolix were 1.4521 [0.9812, 2.1491] and 1.4732 [0.8550, 2.5386], respectively). In patients with severe renal impairment (CL_{cr} 15 to 29 mL/min), the AUC_{0-∞} of relugolix was increased by 1.5-fold and the C_{max} by 1.1-fold (GMR [severe renal impairment/normal renal function] and 90% CI for the AUC_{0-∞} and C_{max} of relugolix were 1.49 [0.9681, 2.2869] and 1.10 [0.6763, 1.7862], respectively). The terminal elimination phase half-life estimate in patients with moderate renal impairment was the same as that in healthy participants with normal renal function (mean half-life estimates of 56.3 hours for both cohorts) and in patients with severe renal impairment slightly shorter (60.2 hours) than that in healthy participants with normal renal function (74.6 hours using the final PopPK model), post-hoc estimated exposures for subpopulations of simulated patients with moderate or severe renal impairment were consistent with results from dedicated clinical pharmacology studies. The post-hoc AUC_{ss} and C_{trough,ss} estimates in patients with mild renal impairment (N = 278) were increased by 1.10-fold (10% increase) and 1.19-fold (19%), respectively, compared with patients with normal renal function (N = 216). The influence of end-stage renal disease with or without hemodialysis on the pharmacokinetics of relugolix has not been evaluated.

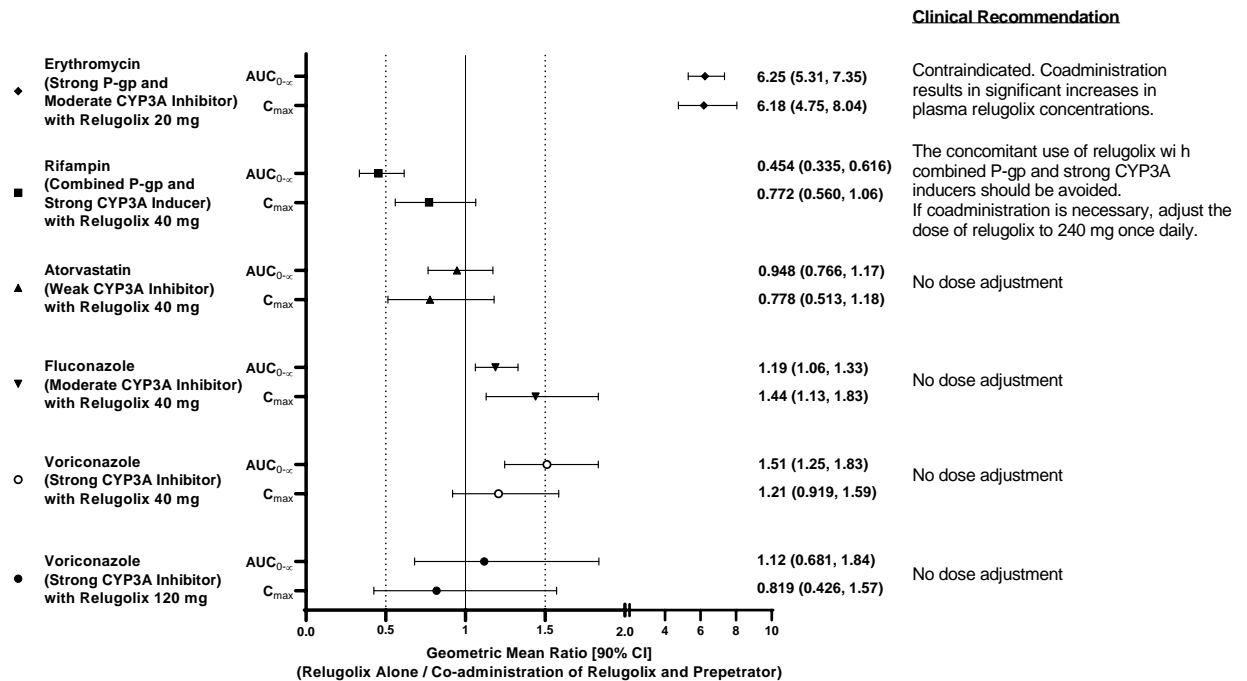
Drug Interactions

Effect of Other Drugs on Relugolix (Victim Interactions)

Because relugolix is a sensitive P-gp substrate, inhibition or induction of intestinal P-gp may increase or decrease the oral bioavailability and exposure to relugolix, respectively. Based on in vitro studies, relugolix was identified as a substrate for CYP3A and CYP2C8.

Four clinical drug interaction studies were conducted to assess the effects of a strong P-gp and moderate CYP3A inhibitor (erythromycin) and a strong CYP3A inhibitor devoid of P-gp inhibition (voriconazole) on the pharmacokinetics of relugolix in order to discriminate between P-gp- and CYP3A-mediated effects. Another study with a weak CYP3A inhibitor (atorvastatin) and moderate CYP3A inhibitor (fluconazole) was conducted (C27005). A study to assess the impact of a P-gp and strong CYP3A inducer (rifampin) also was conducted. Results these studies and clinical recommendations are summarized in [Figure 4](#).

Figure 4: Effect of Other Drugs on the Pharmacokinetics of Relugolix and Clinical Recommendations



Abbreviations: AUC = area under the concentration-time curve; AUC_{0-∞} = AUC from time zero extrapolated to infinity; CI = confidence interval; C_{max} = maximum observed concentration; CYP3A = cytochrome P450 isozyme 3A; P-gp = P-glycoprotein.

Source: Figure 29, Module 2.7.2.

An assessment of the concomitant use of acid-reducing agents on the primary efficacy endpoint of the pivotal phase 3 study in men with advanced prostate cancer (MVT-601-3201) showed that in 162 of the 622 (26.0%) patients in the relugolix group who received a proton pump inhibitor or H₂-receptor antagonist, 100% achieved and maintained castrate levels (< 50 ng/dL) from Day 29 to Day 337 versus 460 of 622 (74.0%) patients in the relugolix group without concomitant use. The majority of acid-reducing agents were proton pump inhibitors and the duration of coadministration of acid-reducing agents with relugolix was 1 to 355 days.

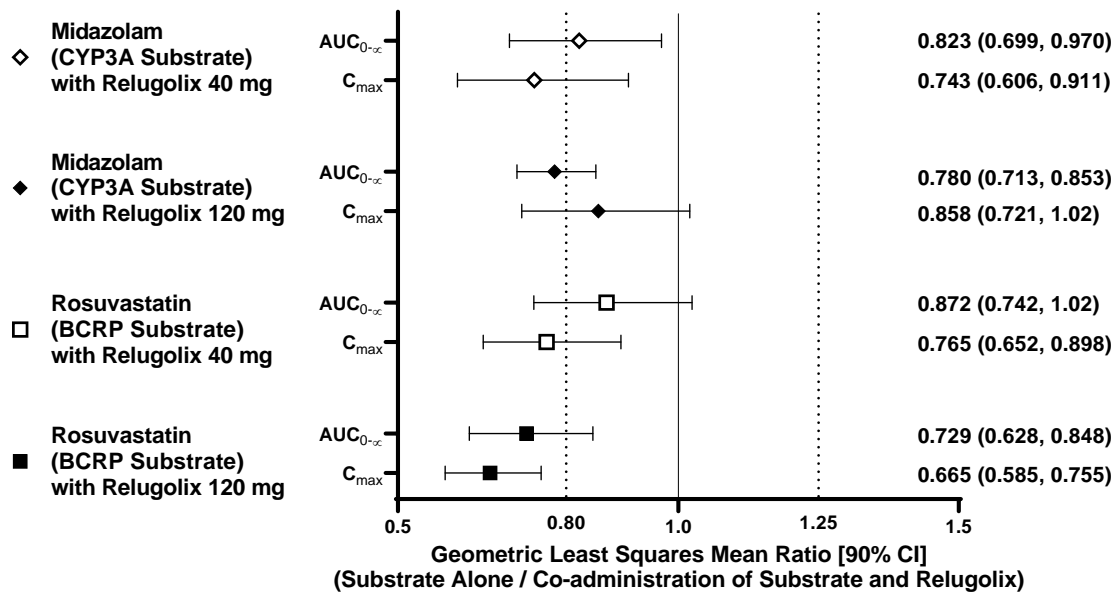
Effect of Relugolix on Other Drugs (Perpetrator Interactions)

At clinically relevant concentrations, relugolix was not a direct time-dependent inhibitor of the major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4) or an inducer of CYP1A2 or CYP2B6, although relugolix was a direct inhibitor and inducer of CYP3A. Relugolix was an in vitro inhibitor of BCRP, and less potently P-

gp, but did not cause inhibition of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, or bile salt extrusion protein at clinically relevant concentrations.

Two drug interaction studies were conducted to assess the effect of relugolix on a sensitive CYP3A substrate (midazolam) and a BCRP substrate (rosuvastatin). Results of these studies and clinical recommendations are summarized in [Figure 5](#).

Figure 5: Geometric Mean Ratios and 90% CI for the $AUC_{0-\infty}$ and C_{max} of Midazolam and Rosuvastatin Upon Coadministration with Relugolix



Abbreviations: AUC = area under the concentration-time curve; $AUC_{0-\infty}$ = AUC from time zero extrapolated to infinity; BCRP = breast cancer resistance protein transporter; CI = confidence interval; C_{max} = maximum observed concentration; CYP3A = cytochrome P450 isozyme 3A.

Source: Figure 31, Module 2.7.2.

The Applicant’s Position:

No dosing modifications for relugolix are required based on age, race, or body size. No dose adjustment for relugolix is required in patients with mild or moderate hepatic impairment or mild, moderate, or severe renal impairment.

The relatively small increase or decrease in exposure to relugolix in patients with mild or moderate hepatic impairment were considered not to be clinically meaningful.

Therefore, no dose adjustments for relugolix in patients with mild or moderate hepatic impairment are required.

Relugolix

Although a 1.5-fold increase in exposure was observed in both patients with moderate or severe renal impairment, the elimination half-lives were similar, supporting a conclusion that neither the presence or degree of renal impairment has an impact on the systemic clearance of relugolix. As a result, upon multiple-dose administration, relugolix is not expected to accumulate to a greater extent in patients with moderate or severe renal impairment than in healthy participants. The 1.5-fold increase in the $AUC_{0-\infty}$ of relugolix observed in patients with moderate and severe renal impairment is not considered to be clinically meaningful based on the safety profile of relugolix where single doses of up to 360 mg and multiple doses of up to 180 mg were generally safe and well tolerated in healthy men or women. Although, based on the upper bound of the 90% CIs for the GMRs of the $AUC_{0-\infty}$, a maximum possible increase in exposure is slightly greater than 2-fold, the central tendency for an increase in exposure is 1.5-fold. Additionally, based on post-hoc exposure estimates, no clinically meaningful increase in exposure in patients with mild renal impairment was observed. Based on these collective assessments, no dose adjustment for relugolix in patients with mild, moderate, or severe renal impairment is required.

Relugolix is a sensitive substrate of P-gp. Coadministration of relugolix with strong P-gp inhibitors is expected to increase the exposure of relugolix in a clinically meaningful manner. Therefore, the proposed prescribing information advises that concomitant use of strong P-gp inhibitors with relugolix is contraindicated. Because an analogous standard classification system based on inhibitor strength has not yet been established for transporters, as has been developed for CYP enzymes, a relative assessment of the effect of inhibitors for other P-gp substrates (dabigatran and digoxin) compared with relugolix was used to identify P-gp inhibitors that would be expected to cause a 2-fold increase in relugolix exposure upon coadministration and are referred to as strong P-gp inhibitors. The specific strong P-gp inhibitors for which concomitant administration with relugolix are contraindicated include: ranolazine, amiodarone, dronedarone, propafenone, quinidine, clarithromycin, erythromycin, gentamicin, tetracycline, ketoconazole, itraconazole, carvedilol, verapamil, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir/voxilaprevir, cobicistat, cobicistat-containing combinations, indinavir, ritonavir, ritonavir-containing combinations, cyclosporine, lapatinib, and vemurafenib.

Coadministration of relugolix with P-gp inducers may reduce the exposure and therapeutic effect of relugolix and should be avoided. It is known that induction of P-gp and CYP3A are co-regulated and is reported in the literature that the effect of inducers on P-gp substrates is generally one strength category less than with CYP substrates. Therefore, a list of combined P-gp and strong CYP3A inducers was devised to provide dosing recommendations for relugolix. The resultant list of specific combined P-gp and strong CYP3A inducers with which concomitant use of relugolix should be avoided includes the following: phenytoin, carbamazepine, apalutamide, rifampin, St. John's Wort.

Relugolix

If concomitant use of a combined P-gp and strong CYP3A inducer with relugolix is necessary, the dose of relugolix should be increased to 240 mg (two 120-mg tablets) taken once daily. After discontinuation of the combined P-gp and strong CYP3A inducer, the recommended 120-mg dose of relugolix once daily should be resumed.

Relugolix may be co-administered with acid-reducing agents because no clinically meaningful interaction was observed in patients receiving these drugs concomitantly.

Based on in vitro and in vivo data, relugolix is not a perpetrator of clinically meaningful drug interactions. Results from the midazolam interaction study indicated that relugolix is a weak inducer of CYP3A-mediated metabolism. The relatively small decreases in exposure to midazolam (AUC and C_{max} decreased by 22% and 14%, respectively, for a 120-mg dose of relugolix) is not expected to be clinically meaningful and likely represents the maximum potential reduction, considering that midazolam is a sensitive substrate. Therefore, the potential decrease for other CYP3A substrates are also not expected to be clinically meaningful. In the rosuvastatin drug interaction study, small decreases in the exposure to rosuvastatin were observed (AUC and C_{max} decreased by 27% and 34%, respectively, for a 120-mg dose of relugolix), although the effect is not considered to be clinically meaningful (clinical management of statins therapy includes titration to desired effects). Extrapolation of the effect to other BCRP substrates cannot be made as the results (a decrease, rather than an increase in exposure) were not expected.

The FDA's Assessment:

FDA agrees with the Applicant that:

1. No dose adjustment is required for age (45 to 91 years), race (Asian [19%], White [71%], Black/African American [6%]), or body weight (41 to 193 kg), since no clinically significant differences in the PK of relugolix were observed based on age, race/ethnicity, or body weight.
2. No dose adjustment of relugolix is required for patients with mild or moderate hepatic impairment (HI). The relugolix exposure changes in patients with mild (31% decrease in AUC_{0-inf}) or moderate HI (5% decrease in AUC_{0-inf}) were not considered clinically meaningful as a 50% decrease in exposure of relugolix is unlikely to have a significant effect on efficacy with respect to percentage of patients achieving castrate levels (< 50 ng/dL) based on the PopPK/PD modeling and simulation.
3. No dose adjustment of relugolix is required for patients with mild, moderate, or severe renal impairment (RI). The 1.5-fold increase in the AUC_{0-inf} of relugolix observed in patients with moderate and severe RI was not considered clinically meaningful, as relugolix was generally safe and well tolerated up to a single dose of 360 mg and multiple doses of 180 mg (1.5 times the recommended 120 mg once daily dosage) in healthy subjects.

Relugolix

4. Co-administration of relugolix with combined P-gp and strong CYP3A inducers should be avoided, as co-administration relugolix with rifampin (a P-gp and strong CYP3A co-inducer) decreased the AUC and C_{max} of relugolix by 55% and 23%, respectively, which may reduce relugolix activity. If coadministration is unavoidable, the maintenance dose of relugolix should be increased to 240 mg once daily.
5. No clinically significant differences in the PK of relugolix were observed when co-administered with voriconazole (strong CYP3A inhibitor), enzalutamide, or acid-reducing agents. No clinically significant differences in the pharmacokinetics of midazolam (sensitive CYP3A substrate) or rosuvastatin (BCRP substrate) were observed when co-administrated with relugolix.

Initially, the Applicant proposed (b) (4)

P-gp inhibitors, as co-administration of relugolix with erythromycin (a P-gp and moderate CYP3A inhibitor) increased the AUC and C_{max} of relugolix by 6.2-fold, which may increase the risk of relugolix adverse reactions. Considering patients with advanced prostate cancer are usually being treated for co-morbid conditions and likely receiving multiple concomitant medications, the Applicant submitted an alternative proposal to avoid co-administration of relugolix with P-gp inhibitors (b) (4)

. If co-administration is unavoidable, the Applicant recommends the following risk mitigation strategies to minimize a potential interaction between relugolix and orally administered P-gp inhibitors:

- Temporary interruption of relugolix administration (for up to 14 days [2 weeks]) for a short-term treatment course with an orally administered P-gp inhibitor dosed more than twice daily (e.g., certain macrolide antibiotics);
- A dose-separation strategy for orally administered P-gp inhibitors with a once or twice daily dosing regimen, where relugolix is administered first followed by administration of the P-gp inhibitor a minimum of 6 hours afterward.

The justifications supporting the proposals are provided as following:

- Temporary discontinuation of relugolix for short-term use of P-gp Inhibitors that are dosed more than twice daily (e.g., erythromycin, clarithromycin):
 - Simulation conducted using the final PopPK/PD model demonstrated that approximately 97.3% and 85.5% of the patients are predicted to maintain testosterone concentrations at castrate levels (< 50 ng/dL) upon an interruption of treatment with relugolix for 7 days and 14 days, respectively.
 - After an interruption of treatment of 7 days or longer, a loading dose of 360 mg should be given to rapidly lower the testosterone concentration when treatment with relugolix is resumed.
- A dose-separation for at least 6 hours for long-term use of P-gp inhibitors with a once daily or twice daily dosage regimen:

Relugolix

- Inhibition of intestinal P-gp efflux is primarily responsible for the increase in exposure to relugolix upon simultaneous administration with a P-gp inhibitor. The AUC_{0-inf} and C_{max} of relugolix after co-administration with erythromycin were increased by 6.2-fold compared with relugolix alone, whereas the mean terminal elimination half-lives ($T_{1/2}$) of relugolix were similar (45.5 hours and 44.4 hours, respectively), further supporting the interpretation that the increase in total exposure (as determined by AUC_{0-inf}) is primarily driven by the increase in oral bioavailability (as reflected by C_{max}) due to inhibition of intestinal P-gp efflux rather than a decrease in systemic clearance (as reflected by the comparable $T_{1/2}$).
- Rapid absorption of relugolix with a median T_{max} of 2.25 hours and the majority of absorption being complete in the early disposition phase of the drug with all post-dose peaks occurred within 5 hours;
- Inhibition of P-gp inhibition occurs by competitive inhibition, which requires the presence of inhibitor molecules locally at the site of the transporter to generate a direct, immediate and transient effect. As a result, the effect of P-gp inhibition decreases as local concentrations of the inhibitor drug decrease. Hence, dose separation is effective when the inhibitor is administered after the absorption phase of the substrate drug is complete.
- Considering that 6 hours is sufficient for gastric emptying and passing through the small intestine, administration of relugolix at least 6 hours prior to a P-gp inhibitor is adequate to minimize the local concentration of P-gp inhibitors at the time when majority of relugolix is being absorbed in the early disposition phase.
- Relugolix is administered once daily with or without food, it is clinically practical for the management of the dose separation strategy.

Though the proposed dose separation strategy is acceptable, observed pharmacokinetic data should be collected to further inform product labeling. A PMC will be issued to assess the effect of P-gp inhibitors when administered after relugolix to further inform dosing strategy when co-administration of relugolix with P-gp inhibitors is unavoidable. Refer to Post-Marketing Requirements and Commitments for details.

6.2.2.3. Outstanding Issues

The Applicant's Position:

There are no outstanding issues pertaining to dosing and therapeutic individualization. The clinical pharmacology program as designed, appropriately informed dosing recommendations and requirements for therapeutic individualization, evaluated the pharmacokinetics of relugolix in healthy participants, men with prostate cancer, and in special populations, determined the ADME profile, mass balance and absolute oral bioavailability of relugolix. The potential effects of covariates (age, race, body size [body mass index and body weight], renal impairment [mild to severe]) on the pharmacokinetics of relugolix in the final PopPK model were assessed by univariate

analyses and the potential effects on relugolix exposure assessed by post-hoc parameter estimate comparisons and/or multivariate simulations, as appropriate. Covariates were further evaluated by simulations performed using an exposure-response (PopPK/PD) model to identify the potential impact of changes in relugolix exposure on testosterone concentrations. The exposure-response model was used to define comparability bounds as acceptance criteria for clinically meaningful changes in exposure to relugolix and to guide dosing recommendations for intrinsic and extrinsic factors.

Pharmacodynamic data was used to inform dose selection and highlighted the importance of including a loading dose for the proposed dosing regimen. Drug interaction studies, along with in vitro data, appropriately guided recommendations for concomitant use with other drugs. A lack of an effect of relugolix on QTc interval prolongation was determined in a thorough QT/QTc study.

The effects of severe hepatic impairment and end-stage renal disease with or without hemodialysis on the pharmacokinetics of relugolix was not evaluated. The ability for hemodialysis to remove relugolix from the blood is therefore unknown.

The FDA's Assessment:

FDA will issue a PMC to assess the effect of P-gp inhibitors when administered after relugolix to further inform dosing strategy when co-administration of relugolix with P-gp inhibitors is unavoidable. Refer to Post-Marketing Requirements and Commitments for details.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

A summary of general pharmacology, pharmacokinetics, and other information for relugolix is provided in [Table 2](#).

Table 2: Summary of General Pharmacology, Pharmacokinetic, and Other Information for Relugolix

PHARMACOLOGY	
Mechanism of Action	Relugolix is an orally active, non-peptide GnRH receptor antagonist that competitively binds to GnRH receptors on gonadotrophic neurons, blocking endogenous GnRH from binding to and subsequent activation of GnRH receptors, preventing the release of LH and FSH from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are considerably reduced, resulting in decreased testosterone production by Leydig cells of the testes.
Pharmacodynamics	After administration of a 360-mg single dose of relugolix in healthy men (C27001 Part 1), mean serum LH and FSH concentrations rapidly declined (within 2 hours postdose) with LH concentrations decreased to a nadir by 24 hours postdose and FSH concentrations decreased throughout the 48-hour sampling period. Mean serum testosterone concentrations also rapidly declined (within 4 hours postdose), reaching a nadir at 36 hours postdose with castrate levels (testosterone < 50 ng/dL) achieved by mean (range) 16 (12 to 24) hours postdose, supporting a 360-mg dose as a loading dose to achieve rapid reduction of testosterone concentrations to castrate levels. Upon multiple-dose administration of 120-mg doses once daily, testosterone concentrations were consistently maintained at castrate levels during treatment.
QT Prolongation	Administration of single 60- or 360-mg doses of relugolix did not prolong the QTcF interval in healthy adult men and women to a level of regulatory concern.
GENERAL INFORMATION	
Bioanalysis	Relugolix was measured using validated HPLC-ESI-MS/MS methods. A summary of the method validation reports is included in Module 5.3.1.4.
Healthy Volunteers vs. Patients	Following administration of relugolix 120 mg once daily, PK parameter values are similar between healthy men and men with prostate cancer based on results of cross-study comparisons, which supports extrapolation of data from clinical pharmacology and biopharmaceutics studies in healthy participants, such as drug interactions, food effect, and the thorough QT/QTc study, to the prostate cancer population. Consistent with this, population (healthy vs. prostate cancer) was not a significant covariate in the population pharmacokinetic analysis.
Therapeutic Dose and Exposure, mean (CV%)	After a 360 mg single dose, C_{max} was 215 (85.9) ng/mL and $AUC_{0-\tau}$ was 985 (75.4) ng·h/mL. After a single 360 mg loading dose on Day 1 and then 120 mg once daily thereafter (steady-state), C_{max} was 70.2 (92.0) ng/mL and $AUC_{0-\tau}$ was 407 (41.3) ng·h/mL.
MTD or Exposure	The no observed effect level for QT and QTc interval prolongation in cynomolgus monkeys was 30 mg/kg. In clinical studies, where relugolix was administered as single doses up to 360 mg and as once daily doses up to 180 mg, a maximum tolerated dose was not reached.
Range of Linear PK	Dose proportionality was assessed by estimating the slope of (ln)PK parameter (C_{max} or AUC) versus (ln)Dose in various studies. Relugolix C_{max} and AUC increased in proportion or greater than in proportion to dose over the single dose range of 60-360 mg and the repeat-dose range of 20-180 mg once daily. Across single dose studies, the slope estimates for C_{max} ranged from 1.096-1.77 and for $AUC_{0-\infty}$ ranged from 1.071-1.71. In one repeat-dose (once daily) study, the slope estimate for C_{max} was 1.466 and for $AUC_{0-\tau}$ was 1.177.
Accumulation at steady state, mean	80 mg once daily: $R(AUC_{0-\tau})$: 2.07, $R(C_{max})$: 1.52 180 mg once daily: $R(AUC_{0-\tau})$: 2.21, $R(C_{max})$: 1.80
ABSORPTION	

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Relugolix

Absolute/Relative Bioavailability, mean (CV%)	11.6% (62.3)
t _{max} , median (range)	2.25 hours (0.50-5.00 hours)
Transporters Involved in Absorption	P-gp
DISTRIBUTION	
Vd/F or Vd (PopPK estimate)	Vc/F: 7053 L, Vp1/F: 11,730 L, Vp2/F: 14,550 L
Plasma Protein Binding (in vitro)	68.2% to 70.8% primarily to albumin
Blood: Plasma Ratio	0.78
METABOLISM	
Metabolic Pathways	In vitro CYP3A > CYP2C8, intestinal microflora
Metabolites	Metabolism is the primary route of elimination through multiple minor biotransformation pathways. There are no major metabolites of relugolix. Metabolites include Metabolite-A (O-desmethyl relugolix; CYP3A), Metabolite-B (hydroxy-relugolix; CYP2C8), Metabolite-C (N-demethoxylated metabolite of relugolix; intestinal microflora metabolism of unabsorbed drug and unchanged relugolix eliminated in bile), as well as several unidentified metabolites, each representing < 1% of total radioactivity in urine, < 3% of total radioactivity in feces, and ≤ 10% of total radioactivity in plasma.
ELIMINATION	
Primary Route of Elimination	Metabolism
Total Clearance	29.4 L/h
Renal Clearance	8.0 L/h
t _{1/2} (effective)	25 h
t _{1/2} (terminal)	60.8 h
EXCRETION	
% of dose excreted as total radioactivity (unchanged drug)	feces: 80.6 (4.2) urine: 4.1 (2.2)
INTRINSIC FACTORS	
Age	Using the final PopPK model, no clinically meaningful difference for the empirical Bayesian-estimated (post-hoc) AUC _{ss} and C _{trough,ss} of relugolix for subgroups above or below the median age (72 years) based on men who participated in the pivotal phase 3 study (MVT-601-3201) were identified; the impact of age on relugolix AUC _{ss} and C _{trough,ss} was small, with median differences ≤ 14% between patients above and below the median age of 72 years.
Sex	Not applicable. Indication is for men with prostate cancer.
Race	Using the final PopPK model, no clinically meaningful difference for the post-hoc AUC _{ss} and C _{trough,ss} of relugolix for the Asian race compared with other racial groups for men who participated in the pivotal phase 3 study (MVT-601-3201) were identified. Based on post-hoc AUC _{ss} and C _{trough,ss} estimates, Black/African American men (N = 30) had approximately 42% higher AUC _{0-τ} and 35% higher C _{trough} of relugolix compared with non-Black/African American men (N = 590). Additionally, the final PopPK model was used to provide exposure estimates for a simulated population (10,000 individuals) based on the demographics in the phase 3 study with resampling to obtain greater precision of the predicted impact of covariate effects on relugolix exposure. Overall, simulated estimates of AUC _{ss} and C _{trough,ss} estimates for Black/African American race were 26% and 16% higher, respectively, compared with

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Relugolix

	non-Black/African American men. The higher exposure to relugolix observed in Black/African American men is not considered clinically meaningful.
Hepatic Impairment GMR (90% CI)	Mild Hepatic Impairment: C_{max} 0.7567 (0.2958, 1.9357); $AUC_{0-\infty}$ 0.6860 (0.3543, 1.3282) Moderate Hepatic Impairment: C_{max} 1.1736 (0.4162, 3.3093); $AUC_{0-\infty}$ 0.9451 (0.4581, 1.9500) No dose adjustment of relugolix is required for patients with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of relugolix has not been evaluated.
Renal Impairment GMR (90% CI)	Moderate Renal Impairment: C_{max} 1.4732 (0.8550, 2.5386); $AUC_{0-\infty}$ 1.4521 (0.9812, 2.1491) Severe Renal Impairment: C_{max} 1.10 (0.6763, 1.7862); $AUC_{0-\infty}$ 1.49 (0.9681, 2.2869) Based on post-hoc AUC_{ss} and $C_{trough,ss}$ estimates from the final PopPK model for men who participated in the pivotal phase 3 study (MVT-601-3201), mild renal impairment did not impact exposure to relugolix; the median post-hoc AUC_{ss} and $C_{trough,ss}$ in patients with mild renal impairment (N = 278) was increased by 1.10-fold (10% increase) and 1.19-fold (19%), respectively, compared with patients with normal renal function (N = 216). The estimated 1.42-fold higher AUC_{ss} in patients with moderate or severe renal impairment (N = 126 [N = 3 severe and N = 123 moderate]) compared to patients with normal renal function (N = 216) is consistent with the effect observed in the dedicated renal impairment studies. The impact of renal impairment on exposure to relugolix is not considered clinically meaningful and no dose adjustment is required. The effects of end-stage renal disease with or without hemodialysis on the pharmacokinetics of relugolix have not been evaluated.
EXTRINSIC FACTORS	
Drug interactions GMR (90% CI)	In vitro relugolix was identified as a substrate of P-gp, CYP3A, and CYP2C8. Relugolix is a sensitive substrate of P-gp. Coadministration of relugolix with erythromycin (strong P-gp inhibitor) increased geometric mean relugolix C_{max} and $AUC_{0-\infty}$ approximately 6.2-fold. Relugolix is contraindicated for use with strong P-gp inhibitors. Coadministration of relugolix with rifampin (combined P-gp and strong CYP3A inducer) decreased geometric mean relugolix C_{max} 23% and $AUC_{0-\infty}$ 55%. Concomitant use of combined P-gp and strong CYP3A inducers should be avoided; if concomitant use is necessary, the dose of relugolix should be increased to 240 mg (two 120-mg tablets) taken once daily. No clinically meaningful changes in relugolix exposure were observed with voriconazole (strong CYP3A inhibitor). Use of relugolix with acid-reducing agents: Relugolix may be administered with acid-reducing agents because no clinically meaningful interaction was observed in patients receiving these drugs concomitantly. Relugolix is not a perpetrator of clinically meaningful drug interactions based on in vitro and in vivo data. In vitro, at clinically relevant concentrations, relugolix was not a direct time-dependent inhibitor of the major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A) or an inducer of CYP1A2 or CYP2B6, although relugolix was a direct inhibitor and inducer of CYP3A. Relugolix was an in vitro inhibitor of BCRP, and less potently P-gp, but did not cause inhibition of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, or BSEP at clinically relevant concentrations. In clinical drug interaction studies, coadministration of relugolix did not significantly alter midazolam (sensitive CYP3A substrate) or rosuvastatin exposures.
Food Effects GMR (fed/fasted) (90% CI)	C_{max} : 0.7859 (0.5288, 1.1679); $AUC_{0-\infty}$: 0.8116 (0.6436, 1.0234). Fed = high-calorie, high-fat breakfast

Abbreviations: (ln) = natural logarithmic function; AUC = area under the concentration-time curve; $AUC_{0-\infty}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{0-\tau}$ = area under the concentration-time curve from time 0 to end of dosing interval, τ ; AUC_{ss} = area under the curve at steady state; BCRP = breast cancer resistance protein; BSEP = bile salt export pump; CI = confidence interval; C_{max} = maximum observed concentration; $C_{trough,ss}$ = trough concentration at steady state; CV = coefficient of variation; CYP = cytochrome P450;

ESI = electrospray ionization; FSH = follicle-stimulating hormone; GMR = geometric mean ratio; GnRH = gonadotropin-releasing hormone; HPLC = high-performance liquid chromatography; LC = liquid chromatography; LH = luteinizing hormone; MATE = multidrug and toxin extrusion; N = number; MS = mass spectroscopy; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; MTD = maximum tolerated dose; PK = pharmacokinetic; P-gp = P-glycoprotein; PopPK = population pharmacokinetic; QTcF = QT-interval with Fridericia correction method; R = ratio; $t_{1/2}$ = half-life; t_{max} = time to maximum concentration; V_c/F = apparent volume of distribution in the central compartment; V_d/F or V_d = volume of distribution; V_{p2}/F = apparent volume of distribution in the second peripheral compartment; vs. = versus.

Source: Module 2.7.1, Table 39 and Appendix 6.13, Module 2.7.2.

The Applicant's Position:

The data generated from the clinical pharmacology program sufficiently characterizes the pharmacokinetics and pharmacodynamic profile of relugolix to guide safe and effective administration of relugolix to patients. Assessments included determination of the ADME profile, mass balance, and absolute bioavailability, effects of intrinsic factors (demographic parameters and special populations) and extrinsic factors on the exposure to relugolix, victim and perpetrator drug interactions and exposure-response relationship. In vitro identification that relugolix is a P-gp substrate facilitated interpretation of absorption-mediated drug interactions and the modest increases in exposure resulting from moderate or severe renal impairment and dose-proportionality. Studies conducted to assess the effects of P-gp inhibitors and inducers on the pharmacokinetics of relugolix, along with exposure-response modeling, guided specific contraindications and dosing recommendations, respectively. Pharmacodynamic data generated in clinical pharmacology studies provided biologic evidence of the mechanism-of-action for relugolix in humans, supported dose selection and provided data for exposure-response modeling. A thorough QT/QTc study demonstrated that a single 360-mg dose, equivalent to the recommended loading dose and 3 times the recommended daily dose, did not prolong the QTc interval.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes, the clinical pharmacology program provides supportive evidence of the effectiveness of relugolix by demonstrating reductions in testosterone concentrations to a therapeutically effective range, supporting dose selection and highlighting the importance of a loading dose. Additionally, the semi-mechanistic and predictive exposure-response model (PopPK/PD) provides a reliable method used to identify clinically meaningful changes in relugolix exposure and demonstrated that efficacy is maintained without meaningful influence from intrinsic or extrinsic factors.

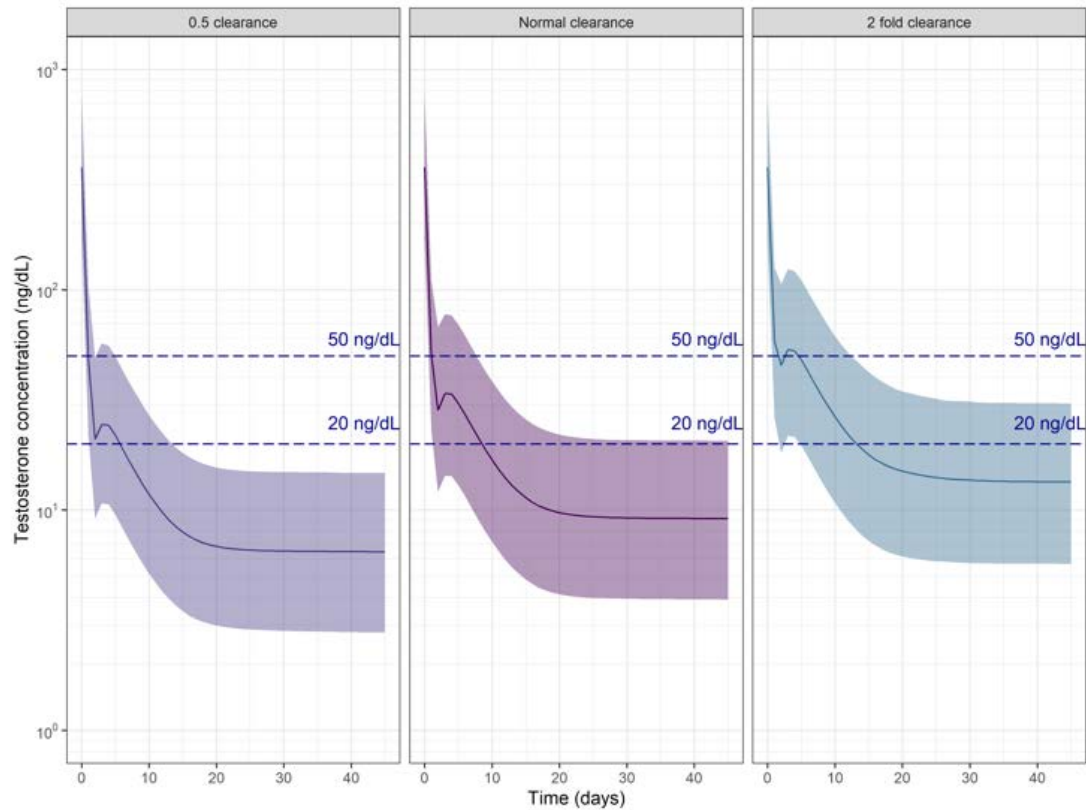
Data:

In the safety, tolerability, pharmacokinetics and pharmacodynamics study in healthy men (C27001), both pituitary hormone (LH and FSH) and testosterone concentrations were rapidly (within hours) decreased after administration of relugolix, with castrate levels achieved within the first 24 hours after a single dose of 360 mg. Upon multiple-dose administration, testosterone concentrations were more consistently suppressed over time at doses greater than 80 mg. Collectively, these data showed the

effectiveness of a loading dose to decrease testosterone concentrations to castrate levels within 24 hours and the importance of daily doses of at least 80 mg to maintain castrate levels of testosterone and supporting the development of a therapeutically-effective dosing regimen (see Section 6.2.2).

The PopPK/PD model was highly predictive of testosterone reductions observed in the pivotal phase 3 study (MVT-601-3201). The PopPK/PD model was used to demonstrate that the 360-mg loading dose followed by 120-mg once daily regimen was the minimum maximally effective dose (see Figure 3) and that a 2-fold increase in clearance resulting in a 50% decrease in exposure to relugolix still maintains efficacy with the upper bound of the 90% CI for testosterone concentrations still below castrate levels (see Figure 6). As a result, despite a 20% decrease in exposure to relugolix with food, efficacy can be maintained. Additionally, these simulations supported dosing recommendations for concomitant use with P-gp inducers (see Section 6.2.2) given the expected decrease in exposure to relugolix associated with P-gp inducers, such that efficacy can be maintained.

Figure 6: Simulated Testosterone Relugolix 120 mg Once Daily, Following a Single Loading Dose of Relugolix 360 mg with Changes in Relugolix Clearance



Notes: Relugolix was administered for 45 days to demonstrate time to reach threshold testosterone concentrations after which testosterone concentrations remain suppressed.

Testosterone concentrations of < 50 ng/dL and < 20 ng/dL represent castrate levels and profound castrate levels.

The shaded area represents the 90% prediction interval of the simulations. The solid lines represent the median of the simulations.

Source: Figure 30, MYOV-PMX-RELUGOLIX-1816 Report 1.

Based on simulation from the final PopPK/PD model, median testosterone concentrations were predicted to achieve castrate levels (< 50 ng/dL) between 24 and 48 hours postdose and profound castrate levels (< 20 ng/dL) between 8 and 9 days after the initiation of treatment for the proposed regimen of relugolix 120 mg once daily, following a single loading dose of relugolix 360 mg on Day 1.

The FDA's Assessment:

FDA agrees with the Applicant that the clinical pharmacology program provides supportive evidence of the effectiveness of relugolix by demonstrating the proposed dosage regimen effectively reduced and maintained the testosterone concentrations

below the castrate levels (< 50 ng/dL). The PopPK/PD modeling and simulation supported the dose selection of a single loading dose of 360 mg on the first day followed by 120 mg once daily. Refer to the FDA's assessment in Section 6.2.2.1. General Dosing for details.

Based on the PopPK/PD modeling and simulation, a 2-fold increase in clearance, which lead to a 50% decrease in exposure of relugolix, is unlikely to have a significant effect on efficacy with respect to percentage of patients achieving castrate levels (< 50 ng/dL). However, more patients will fail to achieve the profound castrate levels (< 20 ng/dL) due to 50% decrease in exposure. In addition, the 2-fold increase in clearance is close to the upper limit of clearance among the subjects used to establish the final PopPK/PD model. Therefore, there is uncertainty in the simulation results and caution should be taken when interpreting the simulation results. FDA used a conservative approach of exposure matching to minimize the risk of potential loss of efficacy. FDA agrees with the Applicant's proposed labeling recommendation that co-administration of relugolix with combined P-gp and strong CYP3A inducers should be avoided, if unavoidable, increase relugolix maintenance dose to 240 mg QD.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes, based on comparison of the exposure to relugolix in healthy subjects and men with prostate cancer, assessment of the potential effects of intrinsic factors (demographics [age, race, and body weight], renal function [mild to severe renal impairment] and hepatic impairment [mild and moderate]), the proposed dosing regimen, 120 mg daily following a loading dose of 360 mg, is appropriate for the patient population for the indication being sought. The pharmacokinetics and exposure to relugolix in healthy subjects and men with prostate cancer were generally similar, indicating that pharmacokinetic and exposure data and exposure-response effects generated in healthy men are expected to be representative of corresponding data in men with prostate cancer. Considering that data from phase 1, phase 2 and phase 3 studies were included in the development of the PopPK and PopPK/PD models, the potential effects of age, race, and body weight on the pharmacokinetics, exposures and exposure-response relationship of relugolix were evaluated over relatively broad ranges. No clinically meaningful effects were identified, indicating that relugolix exposure and testosterone concentrations are expected to be maintained amongst patients with various demographic characteristics. Lastly, no effect on the exposure to relugolix was identified in patients with mild or moderate hepatic impairment or mild, moderate, or severe renal impairment, indicating that the proposed dosing regimen is appropriate for patients whose hepatic or renal function may be compromised. The effects of severe hepatic impairment or end-stage renal disease with or without hemodialysis has not been evaluated.

Data:

The exposure to relugolix (AUC_{0-24} or area under the concentration-time curve from time 0 to end of dosing interval, τ [$AUC_{0-\tau}$], and C_{max}) after administration of a single 360-mg dose (proposed loading dose) or multiple 120-mg doses (proposed daily dose) in healthy men and men with prostate cancer were generally comparable. For example, after administration of a single 360 mg dose, the mean (SD) AUC_{0-24} for relugolix was 1440 (43.4) ng*hr/mL and 985 (75.4) ng*hr/mL in healthy men (C27001) and men with prostate cancer (MVT-601-3201). After once daily administration of 120-mg doses of relugolix, the mean (SD) AUC_{0-24} for relugolix was 367 (67.9) ng*hr/mL in healthy men (MVT-601-044) and 407 (41.3) ng*hr/mL and men with prostate cancer (MVT-601-3201). Although some parameter estimates from other studies were higher or lower, relugolix exposure parameters are highly variable and observed differences are not considered to be clinically meaningful. Importantly, exposure data corresponded to similarly rapid reductions in testosterone concentrations that were maintained over time in both healthy men and men with prostate cancer.

For data supporting assessment of potential effects of intrinsic factors, including demographic parameters (age, race, and body weight) and special populations (mild or moderate hepatic impairment and mild, moderate, or severe renal impairment) on the pharmacokinetics and/or exposure to relugolix, see Section 6.2.2.2.

The FDA's Assessment:

FDA agrees with the Applicant that the proposed dosage regimen is appropriate for the general patient population for which the indication is being sought.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

No, an alternative dosing regimen or management strategy is not required for subpopulations based on intrinsic patient factors.

Data:

See Section 6.2.2.2.

The effect of severe hepatic impairment and end-stage renal disease with or without hemodialysis on the pharmacokinetics of relugolix has not been evaluated.

The FDA's Assessment:

FDA agrees with Applicant that an alternative dosage regimen or management strategy is not required for subpopulations based on intrinsic patient factors. Refer to the FDA's assessment in Section 6.2.2.2. Therapeutic Individualization for details.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food Effect

Relugolix

The Applicant's Position:

No, no clinically meaningful effect of food on the exposure to relugolix was observed.

Data:

See Section 6.2.2.1.

Relugolix as Victim

The Applicant's Position:

Yes, relugolix is a sensitive substrate of P-gp. Upon coadministration of a single 20-mg dose of relugolix with erythromycin, a P-gp and moderate CYP3A inhibitor, the C_{max} and $AUC_{0-\infty}$ of relugolix were increased by 6.2-fold. Therefore, the proposed prescribing information advises that concomitant use of strong P-gp inhibitors with relugolix is contraindicated (see Section 6.2.2.2).

Data:

Coadministration of relugolix with rifampin, a P-gp and strong CYP3A inducer, decreased the C_{max} and $AUC_{0-\infty}$ of relugolix by 23% and 55%, respectively. Coadministration of relugolix with combined P-gp and strong CYP3A inducers may reduce the exposure and therapeutic effect of relugolix. Therefore, the concomitant use of relugolix with a combined P-gp and strong CYP3A inducers should be avoided (see Section 6.2.2.2). If concomitant use of a combined P-gp and strong CYP3A inducer with relugolix is necessary, the dose of relugolix should be increased to 240 mg (two 120-mg tablets) taken once daily. After discontinuation of the combined P-gp and strong CYP3A inducer, the recommended 120-mg dose of relugolix once daily should be resumed.

Relugolix as Perpetrator

The Applicant's Position:

Relugolix is not a perpetrator of clinically meaningful drug interactions.

Data:

See Section 6.2.2.2.

The FDA's Assessment:

FDA agrees with the Applicant that no clinically meaningful effect of food on the exposure to relugolix was observed. Refer to the FDA's assessment in Section 6.2.2.2. Therapeutic Individualization for the evaluation of food effect and drug-drug interactions.

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Yibo Wang
Primary Reviewer

Pengfei Song
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

The clinical development of relugolix 120 mg monotherapy for the treatment of patients with advanced prostate cancer includes 17 studies conducted in healthy participants, patients with hepatic or renal impairment, advanced prostate cancer, intermediate-risk localized disease in combination with radiotherapy, and patients with nonmetastatic prostate cancer.

The primary evidence of efficacy and safety comes from the pivotal phase 3 study MVT-601-3201 in men with advanced prostate cancer requiring one year of ADT. The results of this study are presented and discussed in detail in Section 8.1 and Section 8.2. Efficacy and safety data from the phase 2 study C27003, in men with intermediate-risk, localized prostate cancer requiring 6 months of neoadjuvant/adjuvant ADT with external beam radiation therapy (EBRT), are supportive and included in the assessment of efficacy as appropriate. An overview of these studies is provided in Table 3.

The phase 1 study, TB-AK160108, in patients with nonmetastatic prostate cancer, and the phase 2 study C27002, in patients with advanced prostate cancer were dose-ranging and dose-finding studies, respectively, and which were used to support dose selection (see Section 6). As study C27002 was also conducted in men with advanced prostate cancer, the safety data of C27002 were pooled with that of study MVT-601-3201 and referred to in Section 8.2.

The clinical pharmacology program consisted of 13 studies that assessed the pharmacokinetics of relugolix in healthy participants, the effect of intrinsic and extrinsic factors on the pharmacokinetics of relugolix, including the effects of renal and hepatic impairment and drug interactions, and the potential effect of relugolix on cardiac repolarization (thorough QT/QTc study). A pool of six clinical studies with relugolix monotherapy (b) (4) were included for purposes of providing a broader evaluation of safety, specifically liver safety. The above mentioned 23 studies provide safety data on 2290 patients exposed to relugolix (840 patients with prostate cancer, (b) (4) and 556 participants in clinical pharmacology studies; see Section 8.2).

Table 3: Overview of Clinical Studies Providing the Evidence for Dosing, Efficacy, and Safety for Advanced Prostate Cancer

Protocol No.	No. of Sites/ Locations	Study Design	Population	Objectives	Drug, Dose, Duration	No. of Patients Enrolled (Completed Treatment)	Primary Endpoint(s)
Pivotal Phase 3 Study							
MVT-601-3201/ NCT No. 03085095 Primary analyses (Cohort 1) completed (26 Mar 2020) Final analyses (Cohort 2) is ongoing (b) (4)	155/North and South America, Europe, and the Asia Pacific Region	Multinational, randomized, open-label, parallel-group study	Men aged 18 years or older with androgen- sensitive advanced prostate cancer who are candidates for at least 1 year of continuous androgen deprivation therapy	Efficacy and safety	<u>Relugolix</u> Relugolix 360 mg on Day 1 then 120 mg QD for 48 weeks <u>Leuprolide</u> Leuprolide 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) 3-M depot injection for 48 weeks	<u>Relugolix</u> 624 (563 ^a) <u>Leuprolide</u> 310 (276 ^a)	Cohort 1, primary analyses: To determine whether the sustained castration rate from Day 29 through 48 weeks of treatment for relugolix is greater than or equal to 90%

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Protocol No.	No. of Sites/ Locations	Study Design	Population	Objectives	Drug, Dose, Duration	No. of Patients Enrolled (Completed Treatment)	Primary Endpoint(s)
Key Supporting Studies							
C27003/ NCT No. 02135445 (Phase 2) Completed (21 Nov 2016)	23/US and UK	Two-arm, randomized, active-control, open-label, parallel-group study	Males 18 years or older with intermediate- risk, localized prostate cancer requiring 6 months of neoadjuvant/ad juvant ADT with EBRT	Efficacy, safety, and tolerability	<u>Arm 1</u> Relugolix 320 mg on Day 1 then 120 mg QD for 24 weeks <u>Arm 2</u> Two degarelix 120 mg SC depots on Day 1 then degarelix 80 mg SC depot Q4W starting on Week 5, Day 1	<u>Arm 1</u> 65 (63) <u>Arm 2</u> 38 (38)	Castration rate (< 50 ng/dL from Week 5 Day 1 through Week 25 Day 1)
C27002/ NCT No. 02083185 (Phase 2) Completed (05 May 2017) CSR addendum (01 Dec 2018)	23/US and Canada	Three-arm, randomized, open-label, parallel-group dose-finding study of relugolix, with a leuprorelin observational cohort	Males 18 years or older with advanced hormone- sensitive prostate cancer requiring first- line ADT	Efficacy, safety, and tolerability	<u>Arm 1</u> Relugolix 320 mg on Day 1 then 80 mg QD for 48 weeks ^b <u>Arm 2</u> Relugolix 320 mg on Day 1 then 120 mg QD for 48 weeks ^b <u>Arm 3</u> Leuprorelin 22.5 mg depot Q12W for 48 weeks	<u>Arm 1</u> 56 (31) <u>Arm 2</u> 54 (26) <u>Arm 3</u> 24 (20)	Castration rate (< 50 ng/dL from Week 5 Day 1 through Week 25 Day 1)

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Protocol No.	No. of Sites/ Locations	Study Design	Population	Objectives	Drug, Dose, Duration	No. of Patients Enrolled (Completed Treatment)	Primary Endpoint(s)
TB-AK160108/ NCT No. 02141659 (Phase 1) Completed (05 Dec 2017)	7/Japan	Two-part, open-label, dose -range- finding study	Hormone treatment- naïve Japanese men (20 or more years of age) with nonmetastatic prostate cancer	To evaluate the tolerability, safety, PK, and PD of relugolix alone in hormone treatment- naïve Japanese patients with nonmetastatic prostate cancer	<u>Part A Cohort 1</u> Relugolix 320 mg on Day 1 then 80 mg QD on Days 2 to 28 <u>Part A Cohort 2</u> Relugolix 320 mg on Day 1 then 120 mg QD on Days 2 to 28 <u>Part A</u> (b) (4) Relugolix 320 mg on Day 1 then 160 mg QD on Days 2 to 28 <u>Part A</u> (b) (4) Relugolix 360 mg on Day 1 then 120 mg QD on Days 2 to 28 <u>Part B 80 mg</u> Relugolix 320 mg on Day 1 then 80 mg QD on Day 2 to Week 48 ^b <u>Part B 120 mg</u> Relugolix 320 mg on Day 1 then 120 mg QD on Day 2 to Week 48 ^b	<u>Part A:</u> <u>Total: 13 (12)</u> Cohort 1: 3 (3) Cohort 2: 4 (3) (b) (4) 3 (3) Cohort 4: 3 (3) <u>Part B</u> <u>Total: 30 (26)</u> 80 mg: 15 (13) 120 mg: 15 (13)	<u>Part A:</u> Safety: DLTs, AEs, clinical laboratory tests, vital signs, and 12-lead ECGs <u>Part B:</u> Safety: AEs, clinical laboratory tests, vital signs, and 12-lead ECGs

Abbreviations: 3-M = 3 month; ADT = androgen deprivation therapy; AE = adverse event; DLT = dose-limiting toxicity; EBRT = electron beam radiation therapy; ECG = electrocardiogram; FSH = follicle-stimulating hormone; LH = luteinizing hormone; NCT = National Clinical Trial; PD = pharmacodynamic; PK = pharmacokinetic; Q12W = every 12 weeks; Q4W = every four weeks; QD = once daily; SC = subcutaneous; UK = United Kingdom; US = United States.

^a Number of patients in the primary analysis cohort (ie, completed 48 weeks of treatment).

^b Patients completing 48 weeks of relugolix treatment in study TB-AK160108 and in study C27002 (Arm 1 and Arm 2 had the option to continue for up to 48 additional weeks (ie, 96 weeks total) at their originally assigned relugolix dose levels.

The Applicant's Position:

The 17 studies conducted in healthy participants, patients with hepatic or renal impairment, advanced prostate cancer, intermediate-risk localized disease in combination with radiotherapy, and patients with nonmetastatic prostate cancer that make up the clinical development of relugolix 120 mg monotherapy for the treatment of patients with advanced prostate cancer, provide substantial evidence in the evaluation of dosing, efficacy, and safety for review of the application.

The FDA's Assessment:

The primary evidence of efficacy and safety comes from the pivotal phase 3 study MVT-601-3201. Other trials conducted by the Applicant are considered supportive.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. MVT-601-3201

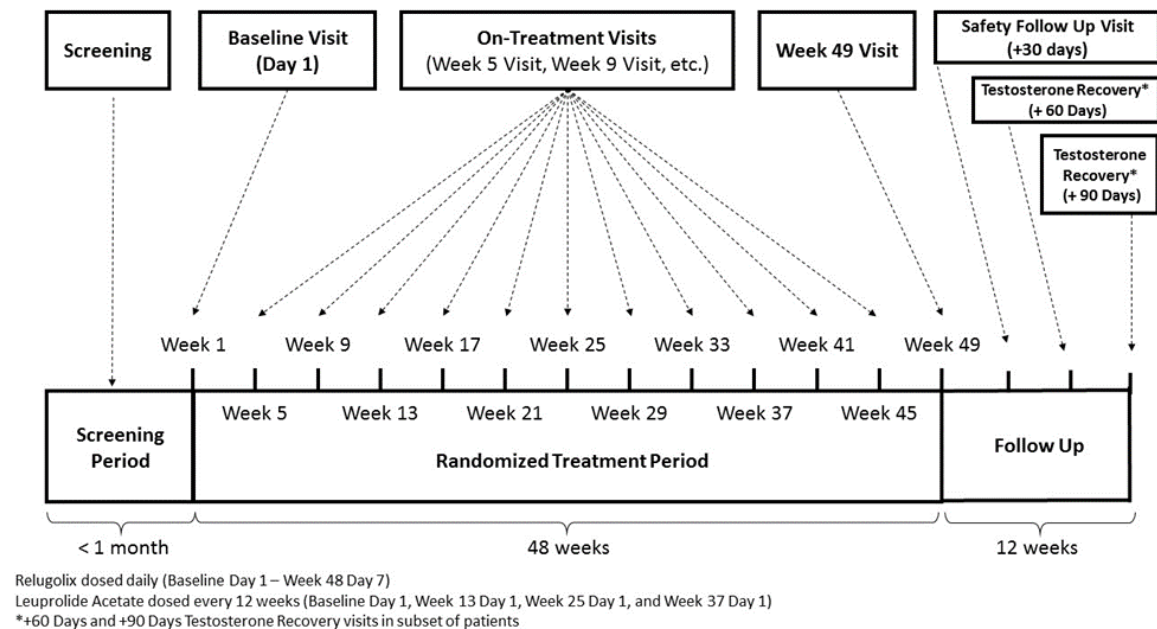
Trial Design

The Applicant's Description:

Study MVT-301-3201 was designed to support registration in multiple regions around the world. This pivotal study is a phase 3 multinational randomized, open-label, parallel-group study to evaluate the safety and efficacy of oral relugolix 120 mg once daily after a single oral loading dose of relugolix 360 mg on Day 1 or leuprolide as 3-month depot suspension 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) every 12 weeks for 48 weeks in patients with androgen-sensitive prostate cancer who require at least 1 year of continuous ADT. The study consists of a screening period of up to 28 days, a treatment period of 48 weeks, and a follow-up period of 30 days. A subset of patients was followed for up to 90 days to assess testosterone recovery. Additionally, unscheduled follow-up visit(s) were arranged for patients with study-related safety concerns as needed.

A schematic of the overall study design is provided in [Figure 7](#).

Figure 7: Schematic of Study Design (MVT-601-3201)



Source: Figure 1, CSR MVT-601-3201.

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To assess different endpoints, the study was amended through Amendment 3 to allow for two predefined analyses of safety and efficacy: the primary analysis and the final analysis. The primary analysis occurred after approximately 915 patients with metastatic or nonmetastatic advanced prostate cancer randomized to the study had the opportunity to be evaluated for 48 weeks and either have completed the 30-day safety follow-up visit or discontinued early. This population is defined as patient Cohort 1. Results from the primary analysis of this study support this NDA. Of these enrolled patients, approximately 150 patients who completed 48 weeks of treatment and who did not plan to start alternative ADT within the following 12 weeks (or within 24 weeks following the last injection of leuprolide 3-month depot) were to be followed for testosterone recovery for up to 90 days.

The study remains ongoing and the final analysis will occur after a total of approximately 390 patients with metastatic disease have enrolled and have had the opportunity to be evaluated for 48 weeks of study treatment, or discontinued early, and complete the 30-day safety follow-up visit. This population is defined as patient Cohort 2 with results to be reported in a final clinical study report (CSR).



To be eligible for the study, a patient must have been, in the opinion of the investigator, a candidate for at least 1 year of continuous ADT for the management of androgen-sensitive advanced prostate cancer and must not have been a candidate for surgical therapy. Eligible patients included 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 could receive radiation therapy, cryotherapy, or high frequency ultrasound no sooner than 2 months after initiation of ADT. Patients previously treated with taxanes or expected to receive taxanes within 2 months after ADT was initiated, were excluded as were patients with recent use of ADT (3 months) or long cumulative use (> 18 months). Baseline serum testosterone must have been ≥ 150 ng/dL (5.2 nmol/L) to be enrolled.

Patients meeting all eligibility criteria were enrolled in the study and randomized 2:1 to receive either relugolix or leuprolide. After randomization, patients in the leuprolide group could receive an antiandrogen for the first 4 weeks or longer if indicated for disease flare management in the opinion of the investigator. Randomization was stratified by geographic region, presence of metastatic disease (metastases in regional lymph node[s] were considered N1 and were, therefore, stratified as nonmetastatic), and age.

Eligible patients received study drug for 48 weeks. During that time, testosterone and PSA were assessed monthly and patient-reported outcomes were assessed approximately every 3 months during the treatment period and more frequently during the follow-up period. Additional serum endocrine evaluations included: LH, FSH, dihydrotestosterone, and sex hormone-binding globulin. Relugolix pharmacokinetic samples were collected predose at visits throughout the study. Additional intensive pharmacokinetic samples were collected on Day 1 and Week 2 in patients from Japan. Safety assessments included treatment-emergent adverse events, clinical laboratory tests, vital signs, 12-lead ECG, physical examinations, and visual acuity tests.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the design features of the HERO study. The study population as defined by inclusion/exclusion criteria appears acceptable for the Applicant's proposed indication. The FDA communicated to the Applicant prior to study enrollment that a two-arm trial was not necessary for approval if the primary endpoint was the probability of maintenance of castrate testosterone levels (b) (4)

Study Endpoints

The Applicant's Description:

The primary endpoint of study MVT-601-3201 was the sustained castration rate, defined as the cumulative probability of testosterone suppression to < 50 ng/dL while on study treatment from Week 5 Day 1 (Day 29) through 48 weeks. A sustained castration rate for which the lower bound of the 95% CI was $\geq 90\%$ was the trial success criterion (Evaluation Criterion 1) required by the FDA for the primary efficacy endpoint. If the result was statistically significant, the key secondary endpoints were to be analyzed in hierarchical order as shown in Table 4.

Table 4: Primary and Key Secondary Endpoints for Primary Analysis of Study MVT-601-3201

Endpoints	Testing Order
Primary Endpoint	
Sustained castration rate ($\geq 90\%$ in relugolix)	1
Key Secondary Endpoints	
Sustained castration rate (noninferiority of relugolix to leuprolide)	2
Castration rate at Week 1 Day 4	3
Castration rate at Week 3 Day 1	4
Confirmed PSA response rate at Week 3 Day 1	5
Profound castration rate at Week 3 Day 1	6
FSH level at Week 25 Day 1	7

Abbreviations: FSH = follicle-stimulating hormone; PSA = prostate-specific antigen.

Source: Table 4, SAP MVT-601-3201.

Demonstration of noninferiority to leuprolide 3-month depot injection on the cumulative probability of sustained testosterone suppression, (b) (4) as the first key secondary endpoint.

Additionally, three more key secondary endpoints will be tested as part of the final analysis: castration resistance-free survival in patients with metastatic disease, castration resistance-free survival in the modified intent-to-treat (mITT) population (metastatic and non-metastatic disease), and time to testosterone recovery.

Analysis of time to testosterone recovery back to 280 ng/dL at the 90-day follow-up was performed at the time of primary analysis for exploratory purposes without formal testing. Other secondary endpoints (not for hierarchical hypothesis testing) included evaluation of the time course and magnitude of sustained profound castration (testosterone < 20 ng/dL), assessment of timing of testosterone recovery (back to ≥ 50 ng/dL and to ≥ 280 ng/dL or baseline), assessment of PSA response rate and time to PSA progression, FSH levels over time, and the impact of treatment on measures of patient-reported outcomes.

Patient-reported outcome questionnaires (European Organization for Research and Treatment of Cancer [EORTC]-Quality-of-Life Questionnaire C30 [QLQ-C30], EORTC- Quality-of-Life Questionnaire PR25 [QLQ-PR25], and EuroQol 5-Dimension 5-Level Scale [EQ-5D-5L]) were completed by patients at baseline, every 2 to 3 months during the treatment period, and at the 30-day safety follow-up visit). They were also completed in the 60-day and 90-day testosterone recovery follow-up if patients were participating in the testosterone recovery follow-up.

The exploratory efficacy endpoint, overall survival, was defined as time from randomization to date of death due to any cause prior to the study data cut-off date. The Kaplan-Meier method was used to describe survival distributions for each treatment group. Patients were censored at the last contact date prior to the data cut-off date.

Safety assessments included adverse events and physical examinations including visual acuity, vital signs, clinical laboratory tests, and 12-lead electrocardiogram (ECG).

The FDA's Assessment:

The HERO trial was designed as a randomized trial, however the preferred FDA approach to evaluation of GnRH analogues is to consider only whether the single investigational arm demonstrates attainment of a castrate (<50 ng/dL) testosterone (T) level that is maintained until the end of a treatment period. The HERO trial still adequately allows for the demonstration of efficacy since the primary analysis includes the calculation of the Kaplan-Meier estimate of the proportion of patients who achieve

and maintain castrate T levels from Day 28 through the end of the 48 week treatment period, with the lower bound of the 95% confidence interval for this estimate being greater than or equal to 90%.

The first key secondary endpoint of sustained castration rate (non-inferiority test between arms) is not acceptable to the FDA. See the FDA's assessment under the statistical analysis plan and amendments for further comments on this endpoint.

The other secondary endpoints evaluated are considered supportive for this application. The PRO endpoints were not under alpha control and all of the PRO analyses are only considered exploratory.

The FDA notes that additional secondary endpoints, including castration resistance-free survival and time to testosterone recovery, will be tested as part of the final analysis but are not currently available for review.

Statistical Analysis Plan and Amendments

The Applicant's Description:

There are two analyses for this study: a primary analysis and a final analysis. The basis of this application is the primary analysis. The primary analysis of efficacy and safety occurred after approximately 915 patients had been randomized to the study (Cohort 1) and were evaluated for 48 weeks and either have completed the 30-day safety follow-up visit or discontinued early.

Sample Size

Sample size determination for this study was based on the assumptions that the probability of sustained testosterone suppression was 94% and 96% for relugolix and leuprolide, respectively, a 2:1 randomization ratio (relugolix:leuprolide); and a dropout rate of 15%.

- For Evaluation Criterion 1, 610 patients in the relugolix group would 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 a noninferiority margin of (b) (4) % and an overall two-sided type I error rate of 0.05, a total of approximately 915 patients (610 receiving relugolix, 305 receiving leuprolide) will yield at least 99% power to declare the noninferiority of relugolix to leuprolide. The (b) (4) % noninferiority margin for the comparison of relugolix versus leuprolide is based on regulatory precedence of the pivotal assessment of the GnRH receptor antagonist degarelix versus leuprorelin as well as studies of branded GnRH receptor agonist generics.

The primary analysis was performed separately for each evaluation criterion using data collected through 48 weeks after enrollment of approximately 915 patients (Cohort 1).

Primary Efficacy Analysis

The efficacy analyses were conducted using a mITT population, defined as all randomized patients who received at least one dose of study drug, unless otherwise specified in the SAP. Stratification variables were geographic region (Europe, North and South America, or Asia and Rest of World), presence of metastatic disease (yes/no evidence), and age (≤ 75 years old or > 75 years old).

The primary hypotheses associated with two evaluation criteria for the primary endpoint in this study were:

- **Hypothesis 1**, corresponding to Evaluation Criterion 1: the cumulative probability of testosterone suppression to < 50 ng/dL for relugolix while on study drug from Week 5 Day 1 (Day 29) through Week 49 Day 1 (Day 337) is $\geq 90\%$.

Null hypothesis H_{01} : $\pi_R < 0.9$ versus Alternative hypothesis H_{a1} : $\pi_R \geq 0.9$

- **Hypothesis 2**, corresponding to Evaluation Criterion 2: relugolix is noninferior to leuprolide 3-month depot injection, as assessed by the cumulative probability of sustained testosterone suppression with a noninferiority margin of $\text{[REDACTED]}^{(b) (4)}\%$.

Null hypothesis H_{02} : $\pi_R - \pi_L < \text{[REDACTED]}^{(b) (4)}\%$

where π_R and π_L are the sustained castration rates for the relugolix and leuprolide groups, respectively.

The cumulative probability of testosterone suppression to < 50 ng/dL from Week 5 Day 1 (Day 29) through Week 49 Day 1 (Day 337) was estimated for each treatment group using the Kaplan-Meier method. The 95% CI for the Kaplan-Meier estimation was calculated using the exponential Greenwood formula via log-log transformation of the survival function.

Key Secondary Efficacy Analyses (for Hierarchical Hypothesis Testing)

If the result of the primary endpoint was statistically significant, the key secondary endpoints were to be analyzed in a prespecified fixed-sequence to control the overall familywise error rate at a two-sided type I error rate of 0.05.

Changes to Planned Statistical Methods

There were no changes to the planned analysis after database lock. The following additional analyses were performed after the database lock.

Cumulative probability of testosterone recovery (back to > 280 ng/dL) at the 90-day follow-up visit in a subset of patients was to be formally tested after a key secondary endpoint of castration resistance-free survival was tested as part of the prespecified hierarchical testing in the final analysis; however, for the primary analysis, this endpoint was analyzed for exploratory purpose. In the final analysis, if statistical significance is

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met on the key secondary endpoint of castration resistance-free survival in both the metastatic and overall populations, testosterone recovery will be formally tested.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the study endpoints. As noted above, the FDA communicated to the Applicant prior to study enrollment that a two-arm trial was not necessary for approval if the primary endpoint was the probability of maintenance of castrate testosterone levels (b) (4)

The FDA agrees with the sample size calculation based on Hypothesis 1 and the mITT analysis population that included all patients who have received at least one dose of study treatment.

The FDA agrees with the primary analysis of castration rate based on Criterion 1, that allows for demonstration of efficacy based on the Kaplan-Meier estimate of the proportion of patients who achieved and maintained castrate testosterone levels from Day 29 through the end of the 48 week treatment period (Day 337), with the lower bound of the 95% confidence interval for this estimate being greater than or equal to 90% in the relugolix arm.

As pre-specified in the statistical analysis plan, to calculate the castration rate achieved at Day 29 and maintained through Day 337 based on the Kaplan-Meier method, events were defined as including:

- patients with testosterone level above castrate level (≥ 50 ng/dL) between Day 29 through Day 337;
- patients did not reach castrate level at Day 29 or had a missing assessment at Day 29;
- patients with one or more consecutive missed visits and who had a non-castrate assessment immediately after the missed visit(s) were considered as failure at the target day of the earliest missed visit prior to the non-castrate assessment.

The following censoring rules to be used in the primary efficacy analysis were pre-specified in the statistical analysis plan:

- Patients who discontinued from the study prior to Day 29 were censored at Day 29.
- Patients who had one missed visit and had a castrate assessment immediately before and after the missed visit were assumed to be castrated at the missed visit.
- Patients with 2 or more consecutive missed visits and who had a castrate assessment immediately before and after the missed visits were censored at the last available testosterone assessment before the missed visits.

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- Patients who had initiated therapies known to suppress testosterone were censored at the time of last testosterone assessment prior to the initiation of such therapies.
- Otherwise, patients were censored at the last available assessment prior to the follow-up visits, including patients who discontinued from the trial for reasons other than a non-castrate testosterone level.

The FDA had concerns regarding the use of a non-inferiority endpoint in this setting due to (b) (4)

Therefore, the FDA did not accept the non-inferiority test and has communicated this concern to the Applicant at the IND stage. During the NDA review the FDA has reiterated this to the Applicant via an information request that stated the following:

“We would like to reiterate that the non-inferiority test is not acceptable (b) (4) as conveyed to the you in the IND stage correspondence. Furthermore, as you pointed out, different censoring rules have been used in historical studies and the current relugolix study and that would affect the outcome estimates. With those issues, the constancy assumption (i.e., the similarity of the new non-inferiority trial to the historical trials) may not be valid. In the meeting preliminary comments document communicated to you in July 2019, FDA has stated that “Additional analyses that you outline in your Diagram of Testing Order (SAP Figure 2) will be considered exploratory.” As we did not accept the proposed non-inferiority comparison, nothing else can be claimed further on this comparison and in general we do not include results of an un-prespecified endpoint and/or analysis in the product label.”

The FDA also noted that the time to testosterone recovery analysis was to be performed in a subgroup of patients, which was not based on randomization. Therefore, interpretation of the results may be problematic, and no statistical inference can be made. The FDA considers this endpoint as an exploratory endpoint.

Protocol Amendments

The Applicant’s Description:

The original study protocol and three amendments were submitted for review and approval by all IECs/IRBs before implementation.

The primary purpose of Amendment 1 (dated 02 Jan 2018) was to provide clarification regarding entry criteria, prohibited medications, schedule of activities, and update on safety reporting. Amendment 2 (dated 18 Jan 2018) clarified schedule of activities. All patients enrolled under the original protocol and Amendment 2 were part of the primary analysis to assess the safety and efficacy of relugolix in achieving castration within 4 weeks and maintaining it over an additional 44 weeks.

Amendment 3 (dated 23 Oct 2018) included an additional key secondary endpoint of castration resistance-free survival, an important indicator of disease progression, in the final analysis. The protocol allowed enrollment of an additional cohort of approximately 100 patients with metastatic disease (Cohort 2) to ensure an appropriate level of statistical power for the analysis. (b) (4)

The FDA's Assessment:

The FDA agrees with the Applicant's description of protocol amendments to HERO. The protocol amendments outlined above did not appear to bias or confound interpretation of the trial results.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

This study was conducted in accordance with ICH E6 (Guideline for Good Clinical Practice [GCP]), applicable participant privacy requirements, and the ethical principles outlined in the Declaration of Helsinki 2013. Additionally, the study was conducted in accordance with the US Code of Federal Regulations, (b) (4) and applicable local/regional regulations and guidelines regarding the conduct of clinical studies.

The Applicant's Position:

This trial was conducted in accordance with applicable local/regional regulations and guidelines.

The FDA's Assessment:

Please refer to Section 4.1 for discussion of GCP deficiencies. With the exception of the site in question, the FDA agrees with the Applicant's position above.

Financial Disclosure

Data:

All principal investigators signed FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) . See Section 19.2.

The Applicant's Position:

Financial interests and arrangements of principal investigators were appropriately disclosed.

The FDA's Assessment:

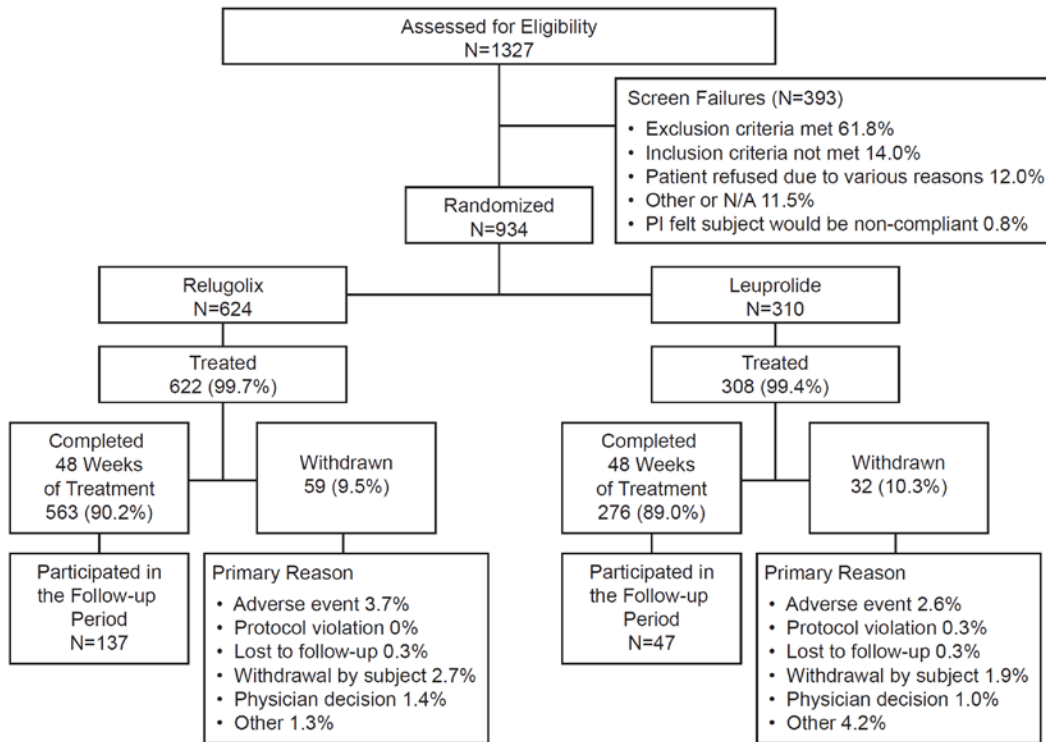
The Applicant disclosed that there was one investigator that had disclosable financial information. Refer to Appendix 19.2 for the FDA’s assessment.

Patient Disposition

Data:

A total of 1327 patients were screened, and 934 patients were randomized at 155 centers globally, including North and South America, Europe, and Asia and Rest of World as part of Cohort 1 to support the primary analysis. The majority of screening failures were due to patients not meeting eligibility criteria, with 61.8% meeting an exclusion criterion and 14% not meeting an inclusion criterion. A further 12% ultimately decided against participation. Figure 8 shows disposition of patients in MVT-601-3201.

Figure 8: Disposition of Patients in Study MVT-601-3201



Abbreviations: N/A = not applicable; N = number of patients.
Source: Figure 2, CSR MVT-601-3201.

The Applicant’s Position:

A total of 624 patients were randomized to receive relugolix and 310 patients were randomized to receive leuprolide. A total of four patients were randomized and not treated (two each in the relugolix and leuprolide groups).

A high proportion of patients completed 48 weeks of treatment in both treatment groups (ie, around 90%). The most common primary reasons for early termination overall were due to adverse events and withdrawal by patient, and both were similar between treatment groups.

The FDA's Assessment:

The FDA agrees with the Applicant's description of patient disposition on HERO. The most common reason for discontinuation in the relugolix arm was an adverse event (3.7%). There does not appear to be a significant impact on the current assessment of patient disposition on this trial based on the number of patients withdrawn.

Protocol Violations/Deviations

Data:

Important protocol deviations were reported for 204 patients (21.9%) (see [Table 5](#)).

Table 5: Summary of Important Protocol Deviations in Study MVT-601-3201 (mITT Population)

	Relugolix (N = 622)	Leuprolide (N = 308)	Total (N = 930)
Any important protocol deviations ^a	126 (20.3%)	78 (25.3%)	204 (21.9%)
Study Treatment Randomization	38 (6.1%)	21 (6.8%)	59 (6.3%)
Concomitant Medication	34 (5.5%)	19 (6.2%)	53 (5.7%)
Informed Consent	16 (2.6%)	11 (3.6%)	27 (2.9%)
Study Procedures/Assessments	12 (1.9%)	11 (3.6%)	23 (2.5%)
Exclusion Criteria	7 (1.1%)	3 (1.0%)	10 (1.1%)
Study Treatment Compliance	7 (1.1%)	3 (1.0%)	10 (1.1%)
Study Treatment Admin/Dispense	9 (1.4%)	0	9 (1.0%)
Other Protocol Deviation	18 (2.9%)	27 (8.8%)	45 (4.8%)

The database lock date was 10 Dec 2019.

Abbreviations: CSR = clinical study report; mITT = modified intent-to-treat; N = number of patients in the treatment group.

Percentages are based on the total number of patients in the modified intent-to-treat population for each treatment group or total.

^a Patients with multiple protocol deviations for a given category or overall are counted only once for each category and overall; therefore, subcategories may not add up to the total.

Source: Table 10, CSR MVT-601-3201.

All categories of important protocol deviations were similar across the two groups, except for "other protocol deviation", which was reported in a higher proportion of patients in the leuprolide group (8.8%) compared with the relugolix group (2.9%). The difference was driven by patients who were not discontinued from study treatment upon having been deemed to have a non-castrate event. When this was identified, a process was successfully put in place that prevented it from happening again.

The most frequent important protocol deviations (6.3%) were categorized as related to treatment randomization procedure and specifically entering of incorrect stratification

factors into the interactive web-response system (IWRS). Almost all errors were related to the stratification of metastatic disease, where patients with only regional lymph node metastases were stratified as patients with metastatic disease in the IWRS. This was subsequently corrected in the electronic case report form (eCRF) and a sensitivity analysis showed no impact on the primary endpoint.

The second most frequent important protocol deviation (5.7%) was related to use of prohibited concomitant medications. Of these, approximately half were due to the use of moderate and strong CYP3A and P-gp inducers or moderate and strong P-gp inhibitors. Except for use of antiandrogens, these concomitant medications were discontinued and, if not in the best interest of the patient, the patient was discontinued from study. Patients who used prohibited concomitant medications did not have a different safety profile. Sensitivity Analysis 2 demonstrated that patients who had received concomitant medications or herbal supplements that could possibly affect testosterone levels had no impact on the primary endpoint analysis.

The Applicant's Position:

Overall, the important protocol deviations were determined to not have impacted the safety of patients, the study integrity, or the efficacy or safety evaluations. Deviations from inclusion and exclusion criteria were not allowed. Myovant oversaw the contract research organization who worked closely with sites to immediately document any inadvertent protocol deviations. Appropriate action was taken to ensure the safety of patients and the integrity and interpretability of the study and study data. Safety and sensitivity analyses of efficacy support the conclusion that the important protocol deviations did not have an impact on the study.

The FDA's Assessment:

Protocol deviations due to stratification factor discordance do not affect the primary analysis, which used a single arm approach. Deviations due to prohibited concomitant medications also likely did not affect the results and is supported by the findings from Sensitivity Analysis 2. Overall, protocol deviations did not appear to impact the results of the HERO trial.

Table of Demographic Characteristics

Data:

The demographic characteristics of the patients in the mITT population are presented in [Table 6](#).

Table 6: Summary of Patient Demographics in Study MVT-601-3201 (mITT Population)

	Relugolix (N = 622)	Leuprolide (N = 308)	Total (N = 930)
Age category (years)			
≤ 75	444 (71.4%)	220 (71.4%)	664 (71.4%)
> 75	178 (28.6%)	88 (28.6%)	266 (28.6%)
Age			
N	622	308	930
Mean (SD)	71.2 (7.75)	71.0 (8.03)	71.1 (7.84)
Median	72.0	71.0	71.0
Min, Max	48, 91	47, 97	47, 97
Race			
Asian	127 (20.4%)	71 (23.1%)	198 (21.3%)
Black or African American	30 (4.8%)	16 (5.2%)	46 (4.9%)
White	434 (69.8%)	202 (65.6%)	636 (68.4%)
Other	8 (1.3%)	7 (2.3%)	15 (1.6%)
Multiple	11 (1.8%)	4 (1.3%)	15 (1.6%)
Not Reported	12 (1.9%)	8 (2.6%)	20 (2.2%)
Ethnicity			
Not Hispanic or Latino	558 (89.7%)	269 (87.3%)	827 (88.9%)
Hispanic or Latino	52 (8.4%)	31 (10.1%)	83 (8.9%)
Unknown	12 (1.9%)	8 (2.6%)	20 (2.2%)
Geographic region			
North America	182 (29.3%)	87 (28.2%)	269 (28.9%)
South America	34 (5.5%)	19 (6.2%)	53 (5.7%)
Europe	247 (39.7%)	122 (39.6%)	369 (39.7%)
Asia	125 (20.1%)	70 (22.7%)	195 (21.0%)
Rest of World	34 (5.5%)	10 (3.2%)	44 (4.7%)

The database lock date was 10 Dec 2019.

Abbreviations: CSR = clinical study report; Max = maximum; Min = minimum; mITT = modified intent-to-treat; N = number of patients in the treatment group; SD = standard deviation.

Note: Percentages are based on the total number of patients in the modified intent-to-treat population for each treatment group or total.

Source: Table 13, CSR MVT-601-3201

The Applicant's Position:

Overall, demographics were similar between the treatment groups, generally representative of the intended target population (ie, patients with advanced prostate cancer), and reflective of a global study. Black or African American men were underrepresented. With 155 participating sites globally, 28.9% of the 930 patients who were enrolled and received drug, were from North America, 39.7% from Europe and 21% from Asia (Japan, South Korea, and Taiwan). The predominant racial representation in the study was White (636 patients [68.4%]). The similarity in baseline characteristics across treatment groups allows for a rigorous statistical comparison.

The FDA's Assessment:

The FDA agrees with the Applicant's description of demographic data for HERO. Characteristics were generally balanced between the two arms. Given that the FDA will not be performing hypothesis tests on the sustained castration rate endpoint between the two treatment arms and will not accept the non-inferiority and superiority claims, the emphasis on evaluation of demographic data is on the patients who received relugolix on HERO. Black patients were underrepresented. A large percentage of patients were Asian due to enrollment in Taiwan and Japan but the significant number of patients enrolled in the U.S. and other sites in Europe are sufficient to adequately capture a patient population that is applicable to the U.S. patient population.

Other Baseline Characteristics

Data:

Disease-specific baseline characteristics of patients in the mITT population are presented in [Table 7](#).

Relugolix

Table 7: Summary of Disease-Specific Baseline Characteristics in Study MVT-601-3201 (mITT Population)

	Relugolix (N = 622)	Leuprolide (N = 308)	Total (N = 930)
Clinical disease state presentation			
Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent	309 (49.7%)	158 (51.3%)	467 (50.2%)
Newly diagnosed androgen-sensitive metastatic disease	141 (22.7%)	70 (22.7%)	211 (22.7%)
Advanced localized disease not suitable for primary surgical intervention with curative intent	172 (27.7%)	80 (26.0%)	252 (27.1%)
Disease stage at study entry ^a			
Metastatic	198 (31.8%)	97 (31.5%)	295 (31.7%)
Locally advanced	189 (30.4%)	95 (30.8%)	284 (30.5%)
Localized	178 (28.6%)	82 (26.6%)	260 (28.0%)
Not classifiable	57 (9.2%)	34 (11.0%)	91 (9.8%)
Gleason score ^b			
2-4	0	1 (0.3%)	1 (0.1%)
5-6	98 (15.8%)	46 (14.9%)	144 (15.5%)
7	237 (38.1%)	122 (39.6%)	359 (38.6%)
8-10	267 (42.9%)	134 (43.5%)	401 (43.1%)
Missing	20 (3.2%)	5 (1.6%)	25 (2.7%)
ECOG status			
0	548 (88.1%)	271 (88.0%)	819 (88.1%)
1	74 (11.9%)	36 (11.7%)	110 (11.8%)
3	0	1 (0.3%)	1 (0.1%)
Prior androgen deprivation therapy			
No	541 (87.0%)	278 (90.3%)	819 (88.1%)
Yes	81 (13.0%)	30 (9.7%)	111 (11.9%)
Had prior radiotherapies			
No	432 (69.5%)	216 (70.1%)	648 (69.7%)
Yes	190 (30.5%)	92 (29.9%)	282 (30.3%)
PSA (ng/mL)			
Mean (SD)	104.150 (415.9588)	68.553 (244.0362)	92.360 (368.2655)
Median	11.685	9.430	10.840
Testosterone (ng/dL)			
N	612	300	912
Mean (SD)	436.07 (158.983)	409.95 (149.070)	427.48 (156.194)
Median	415.76	395.91	407.60

The database lock date was 10 Dec 2019.

Abbreviations: CSR = clinical study report; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form;; mITT = modified intent-to-treat; N = number of patients in the treatment group; PSA = prostate-stimulating hormone; SD = standard deviation; TNM = tumor node metastasis.

Percentages are based on the total number of patients in the modified intent-to-treat population for each treatment group or total.

^aDisease stage at study entry is defined based on TNM stage at study entry, M1 as metastatic, T3/4 NX M0 or N1 M0 and any T N1 M0 as locally advanced, and T1 or T2 N0 M0 as localized. Because the disease stage information was collected on the eCRF, the data were not affected by interactive voice/web recognition system errors.

^bGleason score is determined by adding primary and secondary Gleason scores together.

Source: Table 14, CSR MVT-601-3201.

The Applicant's Position:

Disease-specific baseline characteristics were generally well balanced across treatment groups and were representative of the intended target population for this study as well as for the intended indication (ie, patients with advanced prostate cancer).

The FDA's Assessment:

The FDA agrees with the Applicant's description of disease-specific baseline characteristics in HERO. This advanced prostate cancer population was comprised of patients with metastatic hormone-sensitive prostate cancer, patients with locally advanced disease, and those with localized disease. Nine (9) percent of patients had non-classified disease. Overall, the enrolled patient population is acceptable to support the proposed indication.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Over the course of the study, mean (SD) duration of exposure to study drug was 45.86 (8.34) weeks in the relugolix group and 46.05 (7.41) weeks in the leuprolide group. The proportion of patients with treatment duration > 48 weeks was higher in the leuprolide group (68.2%) compared with the relugolix group (43.2%) due to late leuprolide injections given at the Week 37 Day 1 visit resulting in treatment durations beyond 48 weeks.

The median compliance rate was 100% for the relugolix group and 99.7% for the leuprolide group. Over 99% of patients in each treatment group had an overall compliance rate of ≥ 80%. One patient in the relugolix group and none in the leuprolide group had a compliance rate < 80% (see Section 8.2.2.1, [Table 13](#)).

Overall, 905 patients (97.3%) received at least one concomitant medication during the study, and the proportion of patients who reported taking at least one concomitant medication was 96.6% in the relugolix group and 98.7% in the leuprolide group. The three most frequently reported concomitant medications by Anatomical Therapeutic Chemical classification level 2 term were agents acting on the renin-angiotensin system (50.0%), lipid-modifying agents (42.9%), and antithrombotic agents (39.2%).

A total of 125 patients (13.4%) took at least one concomitant medication or herbal supplement that could possibly affect (increase or decrease) testosterone. More patients in the leuprolide group (30.5%) took at least one therapy compared with the relugolix group (5.0%). Antiandrogens which do not suppress testosterone were the most frequently used in both treatment groups; bicalutamide in the leuprolide group (26.6%) and enzalutamide in the relugolix group (2.7%). For the majority of patients in the leuprolide group, bicalutamide was initiated in the first 4 weeks for the prevention of initial flare (23.1%). Enzalutamide use in the leuprolide group (1.9%) was similar than

in the relugolix group, as it was allowed in the protocol after patients demonstrated radiographic, clinical, or PSA progression.

Overall, 15 patients (1.6%) took at least one therapy known to suppress testosterone during treatment, and all of these patients were in the leuprolide group. All patients who started therapies known to suppress testosterone were censored at the time of last testosterone assessment prior to initiation of the therapies.

Overall, 157 patients (16.9%) had radiation therapy during the study. The majority of patients who received radiation therapy after study treatment initiation was in the primary setting without curative intent (9.6% in the relugolix group and 12.0% in the leuprolide group, 10.4% overall).

The Applicant's Position:

Treatment compliance for relugolix in this study was consistent with reported real-world adherence rates between 92% and 96% for the approved oral androgen axis directed therapies used for castration-resistant prostate cancer (Lafeuille et al. 2014; Behl et al. 2017).

In general, use of concomitant medication was similar across treatment groups. Although more patients in the leuprolide group used concomitant medication or herbal supplements that could possibly have affected testosterone, Sensitivity Analyses 2 of the primary- and first key secondary endpoints were performed excluding all such patients and indicated that this did not impact the outcome of these endpoints.

The FDA's Assessment:

Compliance rates for relugolix appeared to be high. The use of concomitant medications that could affect testosterone levels was low (5%) in the relugolix arm, with the most common drug being enzalutamide. A sensitivity analysis excluding these patients in the relugolix arm demonstrated that this did not appear to impact the outcome of the primary endpoint.

Concomitant radiation therapy (RT) was also allowed no sooner than 2 months after initiating ADT. Patients who were not candidates for radiation therapy with curative intent were enrolled but patients with disease progression during the treatment period could receive RT as prescribed by the investigator. In the relugolix arm, 99 patients (15.9%) received RT, most of which was external beam therapy. The most common site of treatment was the prostatic bed. Radiation in this setting is not known to affect measurement of systemic testosterone levels and is unlikely to have meaningfully impacted study results.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Primary Analysis

NDA/BLA Multi-disciplinary Review and Evaluation: NDA 214, 621
Relugolix

Study MVT-601-3201 successfully met its primary efficacy endpoint with a sustained castration rate from Week 5 Day 1 (Day 29) through 48 weeks of treatment with relugolix of 96.7% and the lower bound of the 95% CI \geq 90% (95% CI: 94.9%; 97.9%). The results of the primary analysis shown in [Table 8](#). An overview of the Kaplan-Meier analysis for sustained castration rate is presented by treatment group in [Figure 9](#).

Table 8: Summary of the Primary Endpoint Analysis (mITT Population)

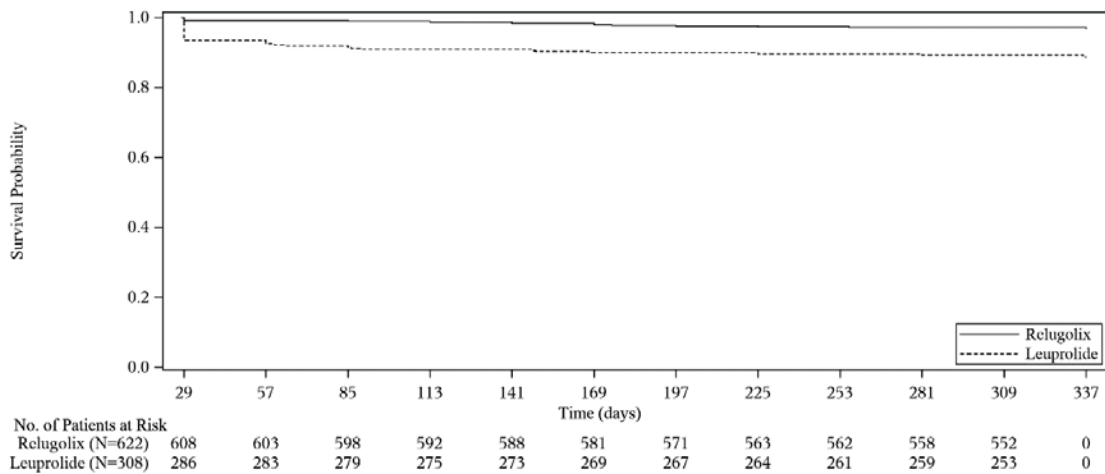
Primary Endpoint	Relugolix (N = 622)	Leuprolide (N = 308)
Sustained castration rate (< 50 ng/dL) from Day 29 through Day 337		
Castration rate at Day 337 (95% CI) ^a	96.7% (94.9%, 97.9%)	88.8% (84.6%, 91.8%)

Abbreviations: CI = confidence interval; CSR = clinical study report; mITT = modified intent-to-treat.

^a 95% CI in each treatment group was calculated by log-log transformation of survival function in each treatment group.

Source: Table 21, CSR MVT-601-3201.

Figure 9: Kaplan-Meier Survival Curve of Sustained Castration Rate (< 50 ng/dL) (mITT Population)



Abbreviations: CSR = clinical study report; mITT = modified intent-to-treat.

Source: Figure 3, CSR MVT-601-3201.

Sensitivity Analyses

A total of four pre-specified sensitivity analyses were conducted to test the robustness of the primary endpoint analysis. The results of these sensitivity analyses are provided in [Table 9](#).

Table 9: Sensitivity Analyses of Kaplan-Meier Estimates for Sustained Castration Rate from Day 29 to Day 337 (MITT Population)

Sensitivity Analysis		Relugolix	Leuprolide	Difference from leuprolide (95% CI) ^b
Sensitivity 1				
Repeated analysis of the primary endpoint using the per-protocol population	N	578	286	
	Day 337 rate	96.5%	89.7%	6.8%
	95% CI at Day 337 ^a	(94.5%, 97.7%)	(85.4%, 92.7%)	(2.9%, 10.7%)
Sensitivity 2				
Analysis excluding patients who received concomitant medications and herbal supplements that could possibly affect testosterone levels during study treatment	N	622	308	
	Day 337 rate	96.9%	89.6%	7.3%
	95% CI at Day 337 ^a	(95.0%, 98.1%)	(84.6%, 93.0%)	(2.9%, 11.7%)
Sensitivity 3				
Analysis with patients who had missed two or more consecutive visits after Week 5 Day 1 or discontinued early from the study considered as an event at the target day of the earliest missed visit	N	622	308	
	Day 337 rate	88.6%	83.7%	5.0%
	95% CI at Day 337 ^a	(85.8%, 90.9%)	(79.0%, 87.4%)	(0.1%, 9.8%)
Sensitivity 4				
Analysis assessing the impact of delayed testosterone suppression to castrate levels. Analysis of the primary endpoint was repeated with the consideration that patients who had not reached castrate levels of testosterone at Week 5 Day 1 were censored at Week 5 Day 1	N	622	308	
	Day 337 rate	97.3%	94.0%	3.3%
	95% CI at Day 337 ^a	(95.6%, 98.4%)	(90.5%, 96.2%)	(0.2%, 6.4%)

The database lock date was 10 Dec 2019.

Abbreviations: CI = confidence interval; CSR = clinical study report; N = number of patients in the treatment group; SD = standard deviation.

^a The 95% CI in each treatment group was calculated by log-log transformation of survival function in each treatment group.

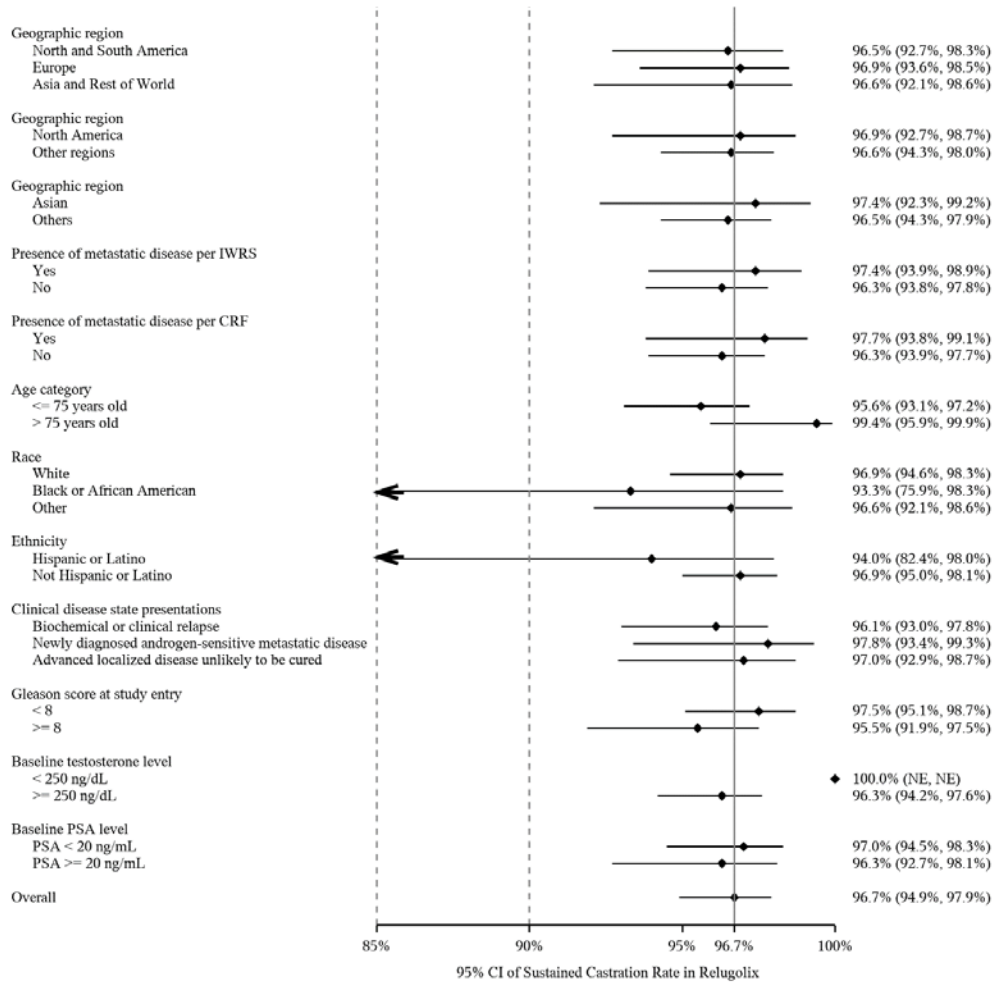
^b The 95% CI for treatment difference was calculated by linear transformation of the difference in survival function.

Source: Section 5.1.1.2 and Table 22 (truncated), CSR MVT-601-3201.

Subgroup Analysis

A forest plot of subgroup analyses for the primary endpoint by predefined selected baseline characteristics and prognostic factors is presented in [Figure 10](#).

Figure 10: Subgroup Analysis for Sustained Castration Rate of Relugolix Patients (mITT Population)



The database lock date was 10 Dec 2019.

Abbreviations: CI = confidence interval; CRF = case report form; CSR = clinical study report; IWRS = interactive voice/web recognition system; mITT = modified intent-to-treat; PSA = prostate-specific antigen.

← : 95% CI of sustained castration rate is extending to 75.9% in Black or African American and to 82.4% in Hispanic or Latino.

Source: Figure 4, CSR MVT-601-3201

The Applicant's Position:

Study MVT-601-3201 met its primary endpoint with the lower bound of the 95% CI of the point estimate (94.9%) above the success threshold of 90%. The robustness of the primary endpoint result was confirmed by multiple sensitivity analyses and was consistent across subgroups.

Results from three of the four sensitivity analyses were consistent with the primary analysis of the primary endpoint exceeding the 90% threshold in the relugolix group. In Sensitivity Analysis 3, both groups were evenly impacted by patients who discontinued early from the study, and despite the lower rates in both groups, the results were generally consistent with those from the primary analysis.

Across all subgroups, point estimates for sustained castration rates for relugolix patients were consistent with the overall estimate of relugolix sustained castration rate observed for the primary endpoint (relugolix castration rate > 90%). In the subgroups of patients of Black or African American race and of Hispanic or Latino ethnicity, the observed wide CIs were driven by the small sample sizes of these subgroups; however, the point estimate was consistent with those observed in other subgroups and the overall population.

The FDA's Assessment:

The FDA agrees with the Applicant that the HERO study met its primary endpoint as demonstrated by the Kaplan-Meier estimate of the proportion of patients who achieved and maintained castrate T levels from Day 28 through the end of the 48 week treatment period, with the lower bound of the 95% confidence interval for this estimate being greater than 90% in the relugolix arm. The detailed information of castration failure and censoring reasons are summarized in Table 10.

Table 10 Summary of Castration Failures and Censoring Reasons

	Relugolix (N=622)	Leuprolide (N=308)
Castration failure events, n (%)	19 (3)	34 (11)
Non-castration T level at Day 29	4 (<1)	17 (6)
Missing D29 assessment	2 (<1)	3 (<1)
Non-castration T level between Day 29 and Day 337	13 (2)	14 (5)
Censored, n (%)	603 (97)	274 (89)
No post baseline assessment	1 (<1)	0
Censored at Day 29 if last assessment prior to Day 29	5 (<1)	2 (<1)
Missing 2 or more consecutive visits (gap > 70 days) ^a	1 (<1)	1 (<1)
Initiation of therapies known to suppress testosterone	0	1 (<1)
Last assessment ^{b, c}	596 (96)	270 (87)

^a The patients had castration T level before and after the missing visits

^b Censored at Day 337 if the last assessment was after Day 337

^c Including patients who initiated therapies known to suppress testosterone after last assessment

[Source: ADTTE.XPT]

The FDA agrees with the Applicant that the point estimates for sustained castration rates appear consistent across subgroups, and confidence intervals are noted to be wide in the subgroups of Black or African American and Hispanic or Latino ethnicity due to the small sample size in these groups.

The FDA also noted that two dosage regimens of leuprolide were used, with the 11.25 mg dose used in Japan and Taiwan and the 22.5 mg dose used at other regions. The 11.25 mg is a dosage regimen that is not recommended for this indication in the US. Of the 308 patients who have received leuprolide, 44 were treated with the 11.25 mg dosage regimen and 264 with the 22.5 mg dosage regimen. The castration rate of the subgroup of patients receiving 22.5 mg leuprolide was 88.0% (95% CI: 83.4%, 91.4%).

Results of sensitivity analyses are consistent with the primary findings observed in the relugolix arm, except that sensitivity analysis #3 had the sustained castration rate estimate lower than 90%. In this sensitivity analysis, patients who had missed 2 or more consecutive visits or discontinued study treatment early were considered as events. In the relugolix arm, a total of 50 additional events were added in this sensitivity analysis. Of the 50 events, one was due to missing 2 or more consecutive visits and the rest were due to early treatment discontinuation. The reasons for early treatment discontinuation in the relugolix arm included adverse events (n=23), withdrawal by patients (n=17), physician's decision (n=6), lost to follow-up (n=2), and other (n=1). Considering early treatment discontinuation as an event is considered as a conservative approach; therefore, the lower sustained castration rate estimated in the sensitivity analysis 3 is not a concern.

Data Quality and Integrity

Data:

The sponsor conducts clinical trials according to GCP and ICH guidelines and conducts a GCP audit program.

A total of 14 investigator site audits were performed by the sponsor. Audit certificates are provided in MVT-601-3201 CSR (Appendix 16.1.8). Sponsor staff provided oversight for contract research organization study monitors who worked closely with investigators and site staff and other vendors contributing to the study conduct.

Data for this study were recorded through an electronic data capture system using eCRFs. The eCRFs were signed by the investigator or by an authorized staff member to attest to the quality and validity of the data.

Accurate and reliable data collection was assured by 100% source document verification and by the maintenance of a drug-dispensing log by the investigator. Discrepancy

reports were generated to address potential corrections and were transferred electronically to the eCRF at the site for resolution by the investigator.

For the central laboratories, documentation of interlaboratory standardization is available in the form of laboratory certifications, reference ranges, and method validation summaries.

The Applicant's Position:

The pivotal phase 3 study supporting this application was conducted according to GCP and ICH guidelines with Sponsor oversight to ensure the safety of subjects and the integrity and interpretability of the study and study data.

The FDA's Assessment:

See Section 4.1 for discussion of GCP deficiencies limited to a single site. The FDA otherwise agrees with the Applicant's position.

Efficacy Results – Secondary Endpoints and Other Relevant Endpoints

The secondary efficacy analyses for study MVT-601-3201 were divided into key or alpha-protected secondary endpoints and other secondary endpoints.

There were six predefined key secondary endpoints to be assessed as part of the primary analysis: noninferiority of relugolix to leuprolide on the rate of sustained castration, the cumulative probability of testosterone suppression to < 50 ng/dL prior to dosing on Week 1 Day 4 (Day 4) and on Week 3 Day 1 (Day 15), the proportion of patients with PSA response at Week 3 Day 1 (Day 15) and confirmed on Week 5 Day 1 (Day 29), the cumulative probability of testosterone suppression to < 20 ng/dL prior to dosing on Week 3 Day 1 (Day 15), and mean FSH concentration at Week 25 Day 1 (Day 169).

If the result of the primary endpoint was statistically significant, the key secondary endpoints were to be analyzed in the prespecified, fixed sequence with the first being noninferiority of relugolix compared to leuprolide. If noninferiority was demonstrated, the other key secondary endpoints were tested in hierarchical order shown in [Table 4](#).

Data:

Key Secondary Efficacy Endpoints

The first key secondary endpoint in the hierarchical testing order was the noninferiority of relugolix compared with leuprolide in sustained castration rate. In comparison with the 96.7% (95% CI: 94.9%, 97.9%) of patients who received relugolix, 88.8% of patients who received leuprolide achieved and maintained sustained testosterone suppression below castrate levels from Week 5 Day 1 (Day 29) to Week 49 Day 1 (Day 337) (95% CI: 84.6%, 91.8%). The between-group difference of 7.9% (95% CI: 4.1%, 11.8%) demonstrated noninferiority of relugolix to leuprolide (the lower bound of the 95% CI for the difference between groups was greater than the prespecified noninferiority

Relugolix

margin of (b) (4) % as well as superiority of relugolix compared with leuprolide (lower bound of the 95% CI greater than zero, with $p < 0.0001$). The (b) (4) % noninferiority margin for the comparison of relugolix versus leuprolide is based on regulatory precedence of the pivotal assessment of GnRH antagonist degarelix versus leuprolide, as well as studies of branded GnRH agonist generics (EMA 2008). The hazard ratio (HR) comparing relugolix with leuprolide for risk of testosterone escape was 0.26 (95% CI: 0.15, 0.46, which excluded 1), indicating relugolix significantly reduced the risk of testosterone escape by 74% compared with leuprolide.

The same four sensitivity analyses used for the primary endpoint were conducted and all four demonstrated both noninferiority and superiority of relugolix to leuprolide. Sensitivity Analysis 4 was conducted to assess the impact of delayed testosterone suppression to castrate levels by Day 29. This analysis censored the 21 patients who had not achieved castrate levels of testosterone at Day 29 (17 in leuprolide and four in relugolix), and the remaining five patients (three in leuprolide and two in relugolix) with missing assessments at Day 29, rather than treating them as having treatment failure events. An estimated 97.3% (95% CI: 95.6%, 98.4%) of patients in the relugolix group achieved and maintained sustained testosterone suppression below castrate levels (< 50 ng/dL) for 48 weeks compared with 94.0% (95% CI: 90.5%, 96.2%) of patients in the leuprolide group.

A subgroup analysis was also conducted for this first key secondary endpoint by the same predefined baseline characteristics and prognostic factors as the primary endpoint. Across all subgroups, except for the subgroup of patients of Black or African American race, differences between groups in sustained castration rates were consistent with the difference observed in the overall population, with the lower bound of the 95% CI for the difference in the sustained castration rate between the two treatment groups greater than the noninferiority margin of (b) (4) %. The Black or African American subgroup (N = 46) was smaller than other subgroups, leading to a wider CI around the between-group difference, limiting the precision of these results.

Because the primary endpoint was met and the first key secondary endpoint was statistically significant, additional key secondary endpoints were therefore tested in the hierarchical order as shown in [Table 10](#).

Table 11: Additional Key Secondary Efficacy Endpoints of Study MVT-601-3201 (mITT Population)

Endpoint	Relugolix (N = 622)	Leuprolide (N = 308)	p-value
Cumulative probability of testosterone suppression to < 50 ng/dL prior to dosing on Week 1 Day 4 (Day 4)	56.040%	0.00%	<0.0001
Cumulative probability of testosterone suppression to < 50 ng/dL prior to dosing on Week 3 Day 1 (Day 15)	98.71%	12.05%	<0.0001
Proportion of patients with PSA response at Week 3 Day 1 (Day 15) followed with confirmation at Week 5 Day 1 (Day 29)	79.4%	19.8%	<0.0001
Cumulative probability of testosterone suppression to < 20 ng/dL prior to dosing on Week 3 Day 1 (Day 15)	78.384%	0.98%	<0.0001
Mean of FSH (IU/L) at Week 25 Day 1 (Day 169)	1.72	5.95	<0.0001

The database lock date was 10 Dec 2019.

Abbreviations: CSR = clinical study report; FSH = follicle-stimulating hormone; mITT = modified intent-to-treat; N = number of patients in the treatment group; PSA = prostate-specific antigen.

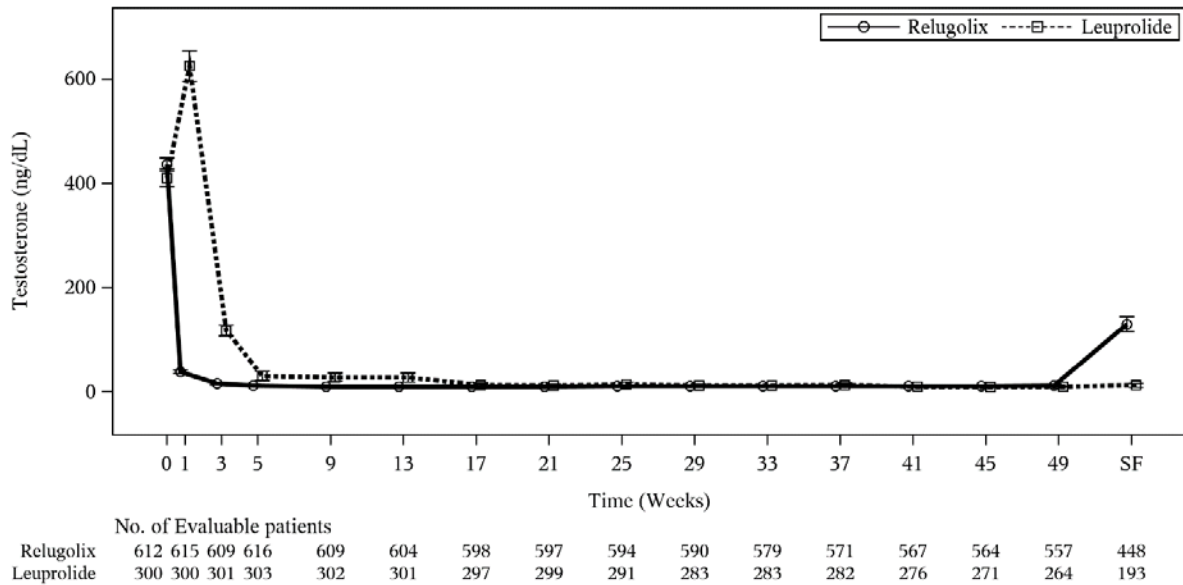
Source: Table 23, CSR MVT-601-3201.

All key secondary endpoints tested demonstrated superiority of relugolix over leuprolide ($p < 0.0001$). A brief summary of other secondary endpoints is provided in the subsequent sections.

Other Secondary Endpoints

Testosterone concentrations over time for the full study period are presented for both relugolix and leuprolide in [Figure 11](#).

Figure 11: Testosterone Concentrations Over Time (mITT Population)



The database lock date was 10 Dec 2019.

Abbreviations: CI = confidence interval; CSR = clinical study report; mITT = modified intent-to-treat; SF = Safety follow up.

Mean (95% CI) are presented.

Source: Figure 6, CSR MVT-601-3201.

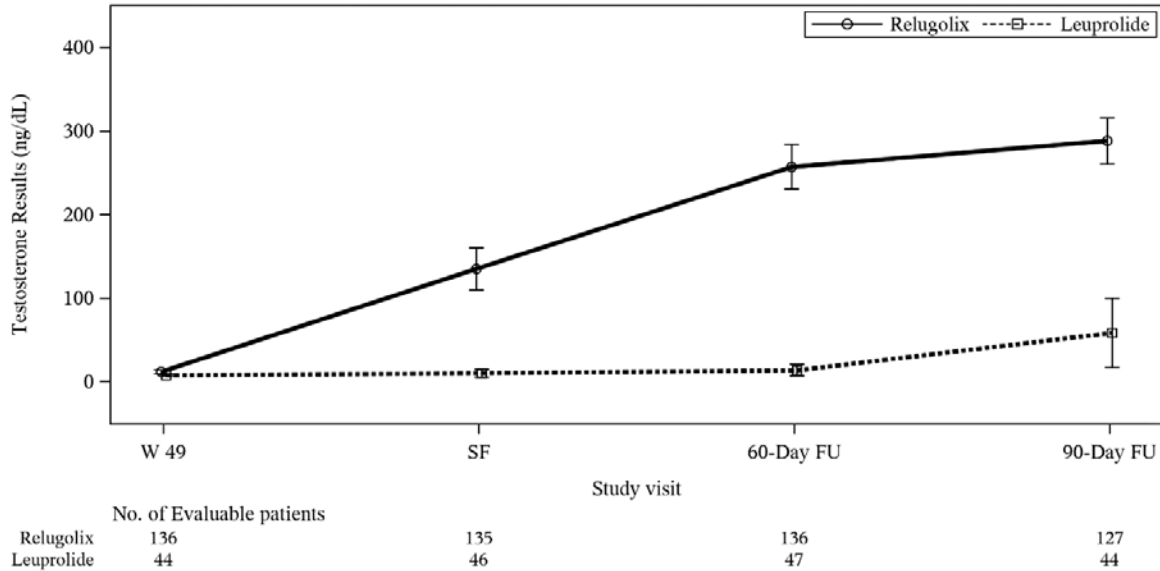
Mean testosterone concentrations decreased rapidly with relugolix treatment and more than 50% of patients reached castrate levels by Day 4. By Day 15, approximately 99% of patients had reached castrate levels and close to 80% achieved profound castration with testosterone concentrations under 20 ng/dL. In contrast, mean testosterone concentrations in the leuprolide group increased rapidly after initiation of treatment, with this initial surge reaching double the baseline concentrations by Day 4. Four weeks after initiation of treatment (ie, Day 29), 99.4% and 95.3% of patients in the relugolix group had testosterone concentrations < 50 ng/mL and < 20 ng/mL, respectively, compared with 82.4% and 56.9% of patients, respectively, in the leuprolide group.

Sustained profound castration rate, defined as the cumulative probability of testosterone suppression to < 20 ng/dL from Day 29 through 48 weeks of treatment, was estimated via the Kaplan-Meier method. The sustained profound castration rate was higher in the relugolix group (81.6%) compared with the leuprolide group (68.6%).

After completing 48 weeks of treatment in study MVT-601-3201, a subset of 184 patients (137 randomized to relugolix and 47 patients, to leuprolide) was followed for testosterone recovery at the 30-, 60-, and 90-day follow-up visits. Time to testosterone recovery back to > 280 ng/dL (lower limit of normal) at the 90-day follow-up visit is an alpha-protected secondary endpoint to be tested in the final analysis.

Testosterone concentrations over 90 days following discontinuation from 48 weeks of study treatment in a subset of patients are shown in [Figure 12](#).

Figure 12: Testosterone Concentrations After Treatment Discontinuation (mITT Population)



The database lock date was 10 Dec 2019.

Abbreviations: CI = confidence interval; CSR = clinical study report; FU = follow-up; mITT = modified intent-to-treat; No. = number; SF = safety follow-up; W = week. Mean (95% CI) are presented.

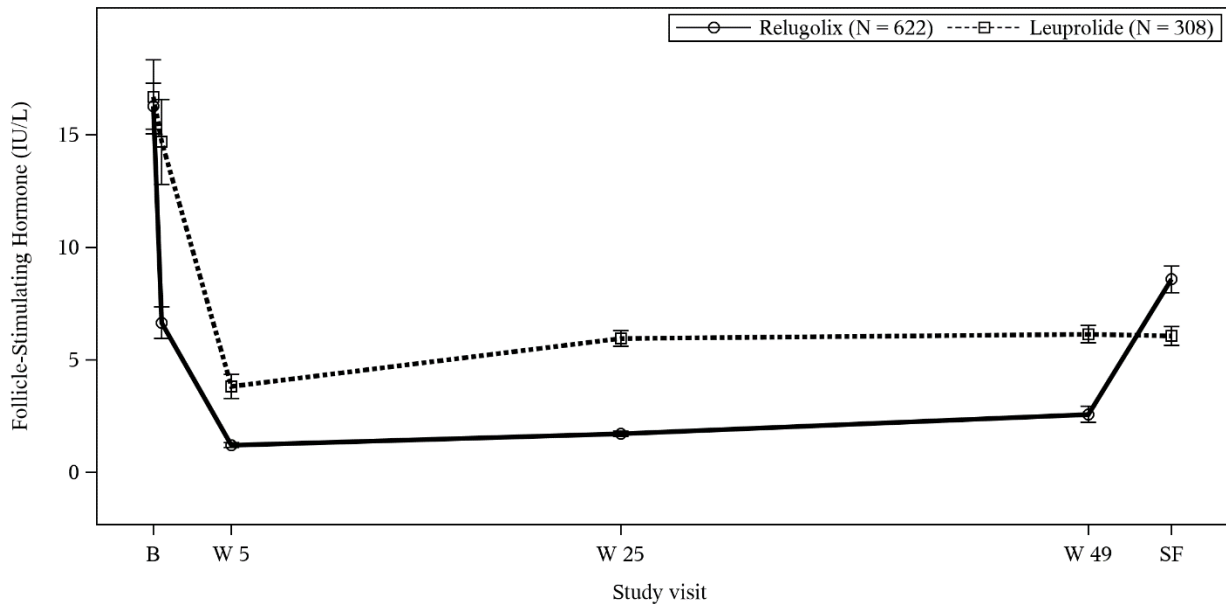
Source: Figure 11, CSR MVT-601-3201.

Patients in the relugolix group began to recover 30 days after study drug discontinuation, compared with patients in the leuprolide group who remained castrated. Time to testosterone recovery was more rapid for the relugolix group compared with the leuprolide group. The cumulative incidence rate of testosterone recovery to > 280 ng/dL at 90 days after discontinuation of study drug was 53.93% in the relugolix group compared with 3.23% in the leuprolide group.

Consistent with the testosterone lowering profile, relugolix was able to rapidly reduce PSA. In the relugolix group, PSA was suppressed more rapidly compared with the leuprolide group, in which an initial increase in PSA was observed. By Day 4, the relugolix group demonstrated a mean 18.58% decrease in PSA from baseline compared with a 5.26% increase in PSA in the leuprolide group.

Follicle-stimulating hormone concentrations over time for relugolix and leuprolide are presented in [Figure 13](#).

Figure 13: Follicle-Stimulating Hormone Concentrations Over Time (mITT Population)



The database lock date was 10 Dec 2019.

Abbreviations: B = baseline; CI = confidence interval; CSR = clinical study report; mITT = modified intent-to-treat; N = number; SF = safety follow-up; W = week.

Mean (95% CI) are presented.

Source: Figure 17, CSR MVT-601-3201.

Follicle-stimulating hormone decreased more rapidly with relugolix compared with leuprolide. At Day 4, the mean FSH decrease from baseline was 62.59% for relugolix compared with 4.74% for leuprolide. In addition, FSH was suppressed to a greater degree by relugolix than by leuprolide at all on-treatment visits; at Week 5 Day 1 (Day 29), Week 25 Day 1 (Day 169), and Week 49 Day 1 (Day 337), mean FSH decrease from baseline was 90.80%, 86.32% and 79.39% for relugolix compared with 67.73%, 47.53%, and 47.23% for leuprolide.

Consistent with the mechanism of action of GnRH receptor antagonists versus agonists, LH concentrations decreased more rapidly with relugolix compared with leuprolide. Baseline mean (SD) LH levels were similar between the relugolix group (7.3 [5.2] IU/L) and the leuprolide group (7.4 [5.8] IU/L). At Day 4, the mean (SD) of the relugolix group decreased to 0.7 (1.0) IU/L compared with the leuprolide group, which increased to 14.9 (7.9) IU/L. At Day 29, the LH in the relugolix group was still slightly lower than the leuprolide group, with leuprolide decreased from baseline values (mean [SD] of 0.3 [0.5] in the relugolix group and 1.2 [2.6] IU/L in the leuprolide group). At a subsequent on-treatment visit (Week 25 Day 1), the mean (SD) LH was similarly suppressed for both the relugolix group (0.3 [0.4] IU/L) and the leuprolide group (0.3 [0.8] IU/L).

Relugolix

The Applicant's Position:

Relugolix achieved the primary endpoint of phase 3 study MVT-601-3201 with a total of 96.7% of patients in the relugolix group achieving castration by Day 29 and maintained it through 48 weeks of treatment (95% CI: 94.9%, 97.9%). In the first key secondary endpoint, relugolix was shown to be superior to leuprolide. The leuprolide group had an 88.8% sustained castration rate (95% CI: 84.6%, 91.8%) with a between-group difference of 7.9% [95% CI: 4.1%, 11.8%]. With the lower bound of the 95% CI being greater than the predefined noninferiority margin of (b) (4) %, relugolix was shown to be noninferior to leuprolide. Furthermore, the lower bound of the 95% CI was above zero, demonstrating the superiority of relugolix to leuprolide ($p < 0.0001$). The robustness of the noninferiority result was demonstrated by sensitivity analyses and were also consistent across a broad range of subgroups.

The key secondary endpoints evaluating the time to testosterone suppression demonstrated the pharmacodynamic action of relugolix as a GnRH receptor antagonist resulted in testosterone suppression earlier than that of the GnRH agonist, leuprolide, as demonstrated by the superior castration rates by Day 4 and by Day 15, each $p < 0.0001$. The profound castration rate in patients receiving relugolix was also superior to that of leuprolide at Day 15 ($p < 0.0001$) and overall, the sustained profound castration rate through 48 weeks was higher in the relugolix group (81.6%) compared with the leuprolide group (68.6%). As expected, suppression in testosterone resulted in greater PSA response rates at Day 15, confirmed at Day 29 for relugolix compared with leuprolide ($p < 0.0001$). In addition, testosterone concentrations in the relugolix group recovered to 280 ng/dL (lower limit of normal) at the 90-day follow-up more rapidly than those in the leuprolide group (nominal $p = 0.0017$).

Finally, relugolix is a non-peptide GnRH receptor antagonist that competitively binds to GnRH receptors on gonadotrophic neurons, blocking their activation and resulting in a decrease of both LH and FSH concentrations, in contrast to GnRH agonists such as leuprolide which suppress LH more completely than FSH. Relugolix achieved greater suppression of FSH at Week 24 than did leuprolide in the pivotal phase 3 study ($p < 0.0001$).

In summary, the key secondary and other secondary endpoints in the pivotal phase 3 study MVT-601-3201 support the primary endpoint analysis and are consistent with the mechanism of action of relugolix, a GnRH receptor antagonist.

The FDA's Assessment:

As noted above, the FDA does not accept the non-inferiority comparison of castration rate between relugolix and leuprolide. Therefore, no claims could be made based on this comparison, including a superiority claim.

The FDA agrees that results of the other key secondary endpoints are supportive of the activity of relugolix. The percentages of patients who attained the castration levels of testosterone < 50 ng/dL and < 20 ng/dL within the first 29 days of treatment are

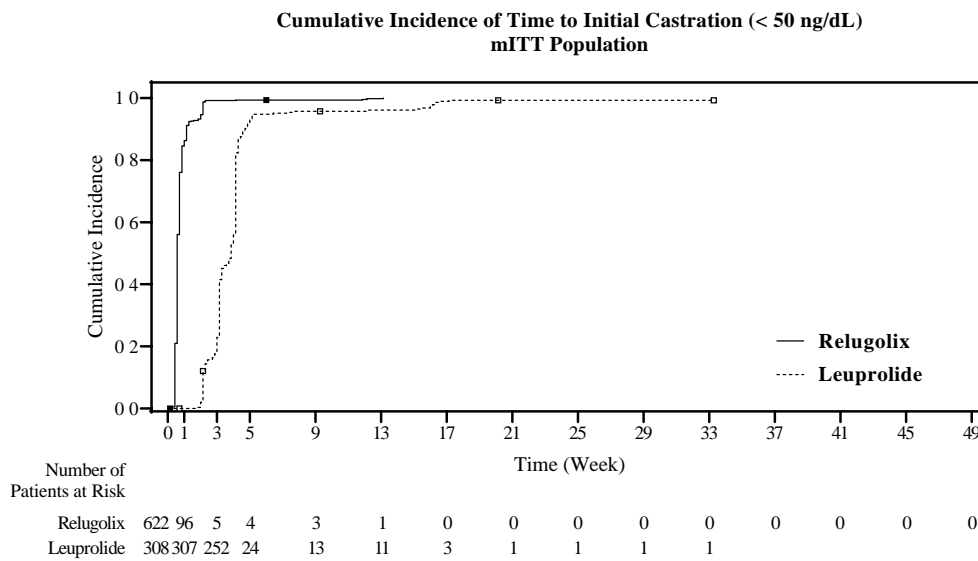
summarized in Table 12 and the cumulative incidences of time to testosterone < 50 ng/dL or < 20 ng/dL are shown in Figure 14 .

Table 12 Percentage of Patients Attaining Testosterone Decreases within the First 29 Days ^a

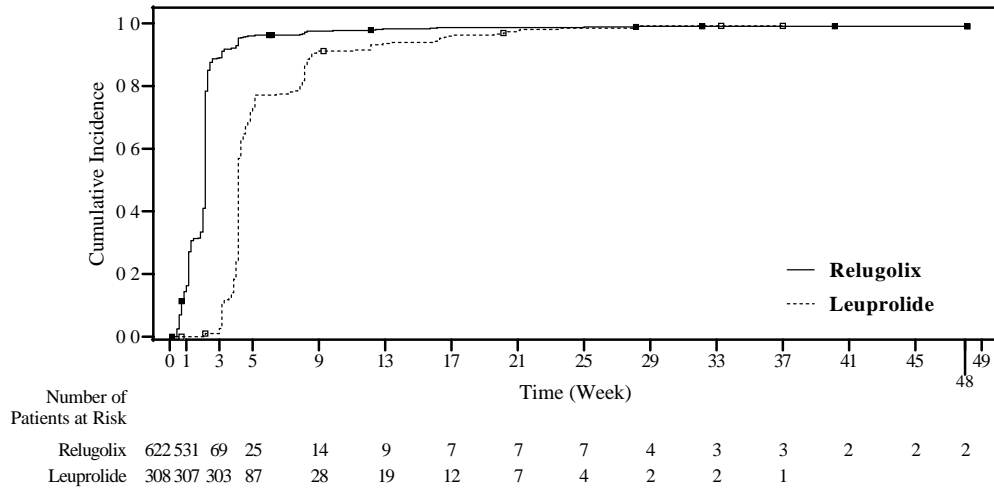
	Testosterone < 50 ng/dL		Testosterone < 20 ng/dL	
	Relugolix (N = 622)	Leuprolide (N = 308)	Relugolix (N = 622)	Leuprolide (N = 308)
Day 4	56%	0%	7%	0%
Day 8	91%	0%	27%	0%
Day 15	99%	12%	78%	1%
Day 29	99%	82%	95%	57%

^a Kaplan-Meier estimates within group.

Figure 14 Cumulative Incidence of Time to Testosterone < 50 ng/dL and Time to Testosterone < 20 ng/dL



Cumulative Incidence of Time to Initial Profound Castration (< 20 ng/dL)
mITT Population



Efficacy Results – Patient-Reported Outcomes

Data:

EORTC-QLQ-C30

In general, there were no notable differences between groups on the EORTC-QLQ-C30 that were clinically meaningful or unexpected in the study. However, this tool was not designed specifically to evaluate patients with prostate cancer.

EORTC-QLQ-PR25

The mean (standard error) score for hormonal treatment-related symptoms domain at the 90-day follow-up visit was lower, indicating less severity, in the relugolix group (-4.3 [0.95]) compared with the leuprolide group (0.2 [1.64]), with a between-group difference of -4.5 (95% CI: -8.0, -1.0). The clinical significance of this reduction is unclear. All other domains in the assessment (urinary symptoms, incontinence aid use, and bowel symptoms) were comparable between the two groups.

EuroQoL EQ-5D-5L

Throughout the study, the proportions of patients who had deterioration, no change or improvement in each domain, were similar across the two groups. The visual analog scores were also similar across the two groups.

The Applicant’s Position:

The only difference in health-related quality of life measures in the testosterone recovery phase observed in study MVT-601-3201 was seen in the EORTC-QLQ-PR25 domains of hormonal-related symptoms. The mean (SD) scores of sexual function and activity were similar between the two groups likely due to the small sample of patients

who responded to the assessment (relugolix, 12 patients) and (leuprolide, 6 patients), and requires further study.

The FDA's Assessment:

There was no pre-specified statistical testing procedure to control for Type 1 error, thus all PRO analyses are considered as exploratory only. No labeling claims can be made based on these results. The FDA sent the Applicant an information request to obtain more information on PRO data from HERO and the Applicant submitted additional information on single items and other aspects of their PRO analyses as requested.

The focus on the FDA analysis is on the relugolix arm. The exploratory analysis of change in physical functioning from baseline over the first year of treatment for the patients who remained on therapy appears to suggest that there was a slight overall decline. However, this change by any previously published thresholds for clinically meaningful change would be considered trivial or small (Cocks 2011).

Regarding results reported for the PR25 instrument, the FDA agrees that the interpretation for the hormonal treatment-related symptoms are unclear and this information was not included in the benefit-risk assessment, as it was also not pre-specified for statistical comparison.

The EQ-5D is not generally considered for the benefit-risk assessment as it is not sensitive to change.

8.1.3. C27003

Trial Design

The Applicant's Description:

C27003 was a phase 2, two-arm, randomized, active-control, open-label, parallel-group study that enrolled patients with a histologically confirmed diagnosis of localized prostate cancer of intermediate prognostic risk for whom 6 months of ADT was indicated as neoadjuvant or adjuvant ADT, with EBRT administered after 12 to 16 weeks of ADT conducted in the US and the UK. Patients were randomized to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every 4 weeks (N = 38) for 24 weeks (after a single loading dose of 240 mg). The degarelix control group was included to provide an observational and contemporary comparison to a depot GnRH peptide antagonist with a mechanism of action similar to that of relugolix.

The FDA's Assessment:

There is a lack of definitive evidence to demonstrate whether short-term ADT with radiation therapy is superior to radiation therapy alone in patients with localized prostate cancer of intermediate risk. Additional questions remain regarding whether ADT is needed when modern high dose radiation therapy is used. The trial design of Study 27003 does not address these issues and thus this study and its results were not considered to be supportive for the use of relugolix in combination with radiation therapy. The FDA did not perform detailed efficacy analysis for this study and this information will not be included in labeling.

Study Endpoints

The Applicant's Description:

The primary endpoint was the rate of effective castration between Week 5 Day 1 (Day 29) to Week 25 Day 1 (Day 169) as determined by the estimated proportion of patients who had testosterone concentrations < 50 ng/dL at all scheduled visits. Secondary endpoints were testosterone and PSA kinetics, changes in prostate gland size, quality-of-life, safety, pharmacokinetics, and pharmacodynamics.

The selected endpoints were appropriate for investigation of ADT in men with advanced prostate cancer. No comparisons between groups were predefined.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the endpoints of Study C27003.

Statistical Analysis Plan and Amendments

The Applicant's Description:

All safety and efficacy analyses were made using the safety population, defined as all patients who received at least 1 dose of any study drug.

Efficacy: Castration rate was estimated using 2-sided 95% CI. Time to castration (< 50 ng/dL), time to profound castration (< 20 ng/dL), the cumulative probability of castration over 24 weeks, and time to testosterone recovery were estimated using the Kaplan-Meier method. Descriptive statistics and absolute and/or percent changes from baseline were used to summarize secondary endpoints (PSA, prostate gland size, quality-of-life measures).

Pharmacodynamics: Serum concentrations of LH, FSH, and sex hormone-binding globulin were summarized over time and presented in line plots by treatment arm and in by-patient listings.

Safety: Safety was evaluated by incidence of adverse events, severity and type of adverse events, and by changes from baseline in the patients' vital signs, weight, and clinical laboratory results.

There were no changes to the planned safety and efficacy analyses.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the statistical analysis plan.

The preferred FDA approach to evaluate castrate rate is using the Kaplan-Meier method, that was used by the Applicant as a sensitivity analysis.

Protocol Amendments

The Applicant's Description:

The protocol was amended twice. The primary rationale for both amendments was to add clarity to study procedures and correct minor errors in the schedule of events.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The amendments were unlikely to have meaningfully impacted study results or interpretation.

8.1.4. Study C27003 Results

Compliance with Good Clinical Practices

The Applicant's Description:

This study was conducted in accordance with ICH E6 (GCP), applicable participant privacy requirements, and the ethical principles outlined in the Declaration of Helsinki

2013. Additionally, the study was conducted in accordance with the US Code of Federal Regulations, (b) (4) and applicable local/regional regulations and guidelines regarding the conduct of clinical studies.

The FDA's Assessment:

The FDA did not conduct inspections for Study C27003 as the results were determined not to be able to be included in labeling and thus the review team cannot comment on GCP compliance.

Financial Disclosure

The Applicant's Description:

All clinical investigators signed a certification/disclosure of financial interests/arrangements. See Section 19.2.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Patient Disposition

Data:

Sixty-five patients in the relugolix group and 38 patients in the degarelix group were included in the Safety Population. Ninety-four (88.7%) patients were enrolled in the US and 12 (11.3%) in the UK. A total of 63 patients (97%) in the relugolix group completed treatment and the study. Of the two patients who did not complete the study, one was lost to follow-up, and one withdrew. All patients (100%) who received degarelix completed their treatment and the study.

The Applicant's Position:

No clinically meaningful differences were noted in disposition between the relugolix and degarelix groups.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Protocol Violations/Deviations

Data:

There were 204 protocol deviations during the study; however, most of these were minor deviations related to out-of-window procedures or missing minor laboratory data. Thirty-four deviations were major, and most were related to missing a safety assessment, which had no major impact on the integrity of the safety or efficacy results of the study. Critical deviations occurred regarding two patients that both met criteria for study discontinuation. Both patients remained in the study and completed treatment per the study protocol.

The Applicant's Position:

The important protocol deviations did not impact the efficacy or safety evaluations.

The FDA's Assessment:

Because the FDA did not perform detailed efficacy analyses for the aforementioned reason, the impact of protocol violations and deviations on the outcomes of this trial have not been assessed.

Table of Demographic Characteristics

Data:

Patient demographics are described in [Table 11](#).

Table 13: Summary of Patient Demographics in Study C27003 (Safety Population)

	Relugolix 120 mg QD (N = 65)	Degarelix 80 mg Q4W (N = 38)
Age (years) ^a		
n	65	38
Mean (SD)	70.2 (5.65)	70.3 (6.97)
Median	71.0	70.5
Min, Max	52, 86	52, 81
Race, n (%)		
White	58 (89)	31 (82)
Black or African American	7(11)	7 (18)
Ethnicity, n (%)		
Hispanic or Latino	2 (3)	3 (8)
Not Hispanic or Latino	62 (95)	35 (92)
Not reported	1 (2)	0

Abbreviations: CSR = clinical study report; Min = minimum, Max = maximum, Q4W = once every 4 weeks, QD = once daily, Std Dev = standard deviation.

Note: Percentages are based on the total number of patients with non-missing value in the Safety Population in each column.

^a Age at date of informed consent.

Source: Table 11.b, CSR C27003

The Applicant's Position:

Demographics were similar between treatment groups and were representative of the intended target population for the study as well as for the intended indication.

The FDA's Assessment:

The FDA agrees that the treatment groups appear similar, however because this intended indication is not being considered, no further analyses or interpretation of demographics were performed during the FDA review for this study.

Other Baseline Characteristics

Data:

Study C27003 enrolled only patients with intermediate-risk, localized prostate cancer requiring 6 months of neoadjuvant/adjuvant ADT to EBRT. The majority of patients in both groups had total Gleason scores of < 8 (69% in the relugolix group and 74% in the degarelix group). The majority of patients in both groups had Eastern Cooperative Oncology Group (ECOG) performance scores of 0 at baseline (92% in the relugolix group and 87% in the degarelix group). Median baseline testosterone and PSA levels were consistent between groups (~12 to 14 nmol/L [~ 346 to 404 ng/dL] and ~7.3 ng/mL, respectively).

The Applicant's Position:

Disease-specific baseline characteristics were representative of the intended target population for this study. All patients had nonmetastatic disease and no evidence of

Relugolix

regional nodal disease, and most patients had Gleason scores < 8, all indicative of a population of patients with intermediate-risk, localized prostate cancer. All patients were deemed by investigators to require 6 months of neo-/adjuvant ADT to EBRT.

The FDA's Assessment:

Because this intended indication is not being considered, no further analyses or interpretation of baseline characteristics were performed during the FDA review for this study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

The imputed method, using investigator/site assessment of patient-reported drug compliance combined with drug accountability (dispensed vs. returned tablets) and patient self-reported dosing compliance using a handheld, electronic, smartphone-like device, which was used only for patients receiving relugolix. Median compliance for both treatments was 100%. The majority of patients (97% in both treatment groups) used at least 1 concomitant medication. The most commonly used concomitant medication was acetylsalicylic acid (46% in the relugolix group and 53% in the degarelix group). Other commonly used concomitant medications included amlodipine, tamsulosin, tamsulosin hydrochloride, lisinopril, and simvastatin.

The Applicant's Position:

Compliance to oral relugolix was high, similar to the depot degarelix injections and consistent to real-world adherence rates for approved oral androgen axis directed therapies (Lafeuille et al. 2014; Behl et al. 2017).

The FDA's Assessment:

Because this intended indication is not being considered, no further analyses or interpretation of these factors were performed during the FDA review for this study.

Efficacy Results

Data:

The primary endpoint for relugolix was met with a 95.4% (95% CI: 87.1%, 99.0%) rate of effective castration. In the degarelix group, the effective rate of castration was 89.5% (95% CI: 75.2%, 97.1%). Testosterone concentrations in both the relugolix and degarelix groups were rapidly reduced to below castrate levels (ie, < 50 ng/dL) within the first week of therapy and those levels were maintained from Week 5 Day 1 (Day 29) to Week 25 Day 1 (Day 169) as is expected for GnRH antagonists. The profound castration rate (testosterone < 20 ng/dL) at Week 25 Day 1 (Day 169) was 81.5% (95% CI:

Relugolix

70.0%, 90.1%) in the relugolix group and 68.4% (95% CI: 51.3%, 82.5%) in the degarelix group.

The percentage PSA reductions and absolute PSA values over time were similar between the relugolix and degarelix treatment groups and consistent with the rapid testosterone reductions observed with both therapies. Follicle-stimulating hormone concentrations were also similarly suppressed between relugolix and degarelix groups during treatment.

Following discontinuation of study drug treatment at the end of Week 24 (or 4 weeks after the final injection of degarelix at Week 21 Day 1), the testosterone recovery profile of relugolix, was differentiated from that of degarelix. At the end of the 12-week follow-up period after study completion, 43.1% (95% CI: 30.8%, 56.0%) of patients who received relugolix had recovered either to the baseline testosterone concentration or to the lower limit of the normal range (> 280 ng/dL), whichever was less, compared with 5.3% (95% CI: 0.6%, 17.7%) of patients who received degarelix.

For quality-of-life assessments, patients reported a larger reduction in hormonal treatment-related symptoms domain of the EORTC-QLQ-PR25 in the relugolix group than in the degarelix group from Week 25 to the end of the study visit, 4 weeks after treatment discontinuation. Median scores for the sexual activity domain did not change from end of treatment to end of study in both relugolix and degarelix groups.

The Applicant's Position:

This phase 2 study in patients with intermediate-risk localized prostate cancer requiring neoadjuvant/adjuvant relugolix to EBRT resulted in a 95% rate of sustained castration.

Both relugolix and degarelix rapidly and profoundly induced and maintained castration during the treatment period. Both relugolix and degarelix resulted in rapid reductions in testosterone concentrations not seen with GnRH receptor agonists, which are associated with an early testosterone flare.

Accordingly, effects on PSA response were consistent between relugolix and degarelix groups. Furthermore, both LH and FSH were fully suppressed while on treatment with both relugolix and degarelix, whereas GnRH receptor agonists do not fully suppress FSH (Shore et al. 2013).

Unlike other androgen deprivation therapies that are injectable, relugolix, an oral non-peptide GnRH receptor antagonist, has the unique advantage of a more rapid testosterone recovery after discontinuation of treatment. Testosterone recovered more rapidly in patients receiving relugolix 12 weeks after treatment discontinuation. These findings are consistent with its pharmacokinetic profile as a daily oral therapy. More rapid testosterone recovery with relugolix was associated with an improvement in a range of castration-related symptoms on quality of life measures. Previous data suggests recovery from degarelix monthly depot injections can take more than 100 days and in this phase 2 study, only 16% of degarelix patients had testosterone recovery 12

weeks after treatment discontinuation (Klotz et al. 2008). Similar delayed recovery of testosterone has been reported with GnRH receptor agonists, particularly with the 3-month depot preparations (Nejat et al. 2000; Murthy et al. 2006).

The FDA's Assessment:

This study does appear to demonstrate that patients receiving relugolix achieved a greater than 95% rate of sustained castration, consistent with the results from the HERO study. However, detailed efficacy analyses were not performed given that use with radiation is not indicated for the aforementioned reasons.

8.1.5. Integrated Review of Effectiveness (supplements only)

The FDA's Assessment:

Not Applicable.

8.1.6. Assessment of Efficacy Across Trials

Evaluation of the efficacy of relugolix was primarily based on the pivotal phase 3 study MVT-601-3201 in men with advanced prostate cancer. In addition to study MVT-601-3201, supportive efficacy data were included from the phase 2 study C27003. Two additional studies were conducted in men with prostate cancer ie, a phase 1 dose-ranging study (TB-AK160108) and a phase 2 dose-finding study (C27002). No pooling of data across studies was performed for the efficacy analyses due to differences in the definition of the primary endpoints and the much smaller study size of the phase 2 and phase 1 studies, relative to the phase 3 study.

Primary Endpoint

Data:

In study MVT-601-3201, a total of 96.7% of patients who received relugolix achieved and maintained sustained testosterone suppression at castrate levels (< 50 ng/dL) from Day 29 through 48 weeks of treatment (95% CI: 94.9%, 97.9%) with the lower bound of the 95% CI exceeding 90% meeting the FDA requirement for demonstration of efficacy and demonstration that relugolix 120 mg adequately achieved and maintained sustained testosterone suppression to castrate levels in more than 95% of men treated. The robustness of these results was confirmed by multiple sensitivity analyses and subgroup analyses.

Results from the phase 2 study C27003 demonstrated that relugolix sustained testosterone suppression in patients with intermediate-risk localized prostate cancer receiving concomitant EBRT, consistent with the findings from study MVT-601-3201. Patients in the relugolix group had a 95.4% (95% CI: 87.1%, 99.0%) rate of effective castration over 24 weeks.

In the dose-finding study C27002 patients in the relugolix group (N = 110) were randomized to receive a maintenance dose of 80 or 120 mg daily after a 320 mg loading

dose on Day 1 and patients in the leuprorelin group received the 22.5 mg 12-week subcutaneous depot (N = 24). The study demonstrated a rapid suppression of testosterone in the relugolix group compared to initial testosterone surge in the leuprorelin group. Effective castration was achieved and maintained from Week 5 Day 1 (Day 29) through 24 weeks of treatment for each treatment group (relugolix 80-mg group, 91.1% [95% CI: 80.4%, 97.0%]; relugolix 120-mg group, 90.7% [95% CI: 79.7%, 96.9%]; leuprorelin group 95.8% [95% CI: 78.9%, 99.9%]).

The Applicant's Position:

The pivotal, phase 3 study MVT-601-3201 successfully met its primary endpoint in patients representing the intended indication of advanced prostate cancer, consistent with efficacy results from the supportive studies in patients with prostate cancer (C27003, C27002, TB-AK160108).

The FDA's Assessment:

The FDA agrees with the Applicant that the primary endpoint of MVT-601-3201 was met. Relugolix adequately achieved and maintained sustained testosterone suppression to castrate levels in more than 95% of men treated, with the 95% CI exceeding 90%.

Secondary and Other Endpoints

Data:

In Study MVT-601-3201, the between-group difference of 7.9% (95% CI: 4.1%, 11.8%) demonstrated noninferiority (the lower bound of the 95% CI for the difference between groups was greater than the prespecified noninferiority margin of ^{(b) (4)} %) as well as superiority of relugolix compared with leuprolide (lower bound of the 95% CI greater than zero, with $p < 0.0001$, a key secondary endpoint). The robustness of these results was confirmed by four sensitivity analyses which all demonstrated both noninferiority and superiority of relugolix to leuprolide. Furthermore, an assessment of this endpoint across multiple subgroups demonstrated that the results are consistent.

All other key secondary endpoints tested, including castration rate on Day 4, castration rate on Day 15, PSA response rate at Day 15, profound castration rate at Day 15, FSH level at Week 25 Day 1, demonstrated superiority of relugolix to leuprolide ($p < 0.0001$).

Study C27003 demonstrated similar results of efficacy endpoints; mean testosterone concentrations rapidly declined without an initial testosterone surge and were at castrate levels by Day 4 in the relugolix group (1.311 nmol/L [37.8 ng/dL]). Furthermore, 97% of patients achieved a PSA reduction of > 50% by the Week 13 Day 1 visit, with PSA declining further through 24 weeks of treatment. A similar degree of FSH suppression was observed for both relugolix and degarelix, with median FSH levels of 0.75 IU/L and 0.70 IU/L at Week 25 Day 1, respectively. This is in contrast to the incomplete suppression of FSH observed with the GnRH receptor agonist, leuprolide, in studies MVT-601-3201 and C27002.

Relugolix

The dose-finding study C27002 similarly demonstrated a rapid testosterone suppression and PSA response with similar suppression of FSH and LH levels for both the relugolix 80 mg and 120 mg groups.

In the dose ranging phase 1 study TB-AK160108, relugolix demonstrated rapid serum testosterone-lowering effects and the ability to maintain serum testosterone concentrations below the castrate level (< 50 ng/dL) through 96 weeks. Similarly, mean and median PSA levels steadily declined for both relugolix treatment groups (80 and 120 mg) through the end of the study.

Mean testosterone concentrations assessed 90 days after treatment discontinuation in the testosterone recovery subset (N = 184) of phase 3 study MVT-601-3201 were 288.4 ng/dL in the relugolix group compared to 58.6 ng/dL in the leuprolide group. The 90-day testosterone recovery rate to ≥ 280 ng/dL was 54% in the relugolix group and 3% in the leuprolide group. Studies C27003 and C27002 similarly demonstrated recovery of testosterone concentrations to above the baseline or castration threshold, respectively, 12 weeks after discontinuation of relugolix.

The Applicant's Position:

In line with its mechanism of action as a GnRH receptor antagonist, relugolix rapidly suppressed testosterone to castrate levels (< 50ng/dL) and profound castrate levels (< 20 ng/dL) without an initial testosterone surge as seen with GnRH receptor agonists. Prostate-specific antigen response was more rapidly achieved with relugolix than with leuprolide. As previously reported for GnRH receptor antagonists and seen in study C27003, relugolix and degarelix more profoundly suppressed FSH levels compared with leuprolide. Unique to the oral formulation and in contrast to the depot injections, relugolix demonstrated a rapid testosterone recovery upon discontinuation of ADT. The consistency of results across relugolix studies demonstrate the robustness of the results.

The FDA's Assessment:

The secondary endpoints are considered supportive of the efficacy of relugolix. The effects on FSH and LH are consistent with the mechanism of action of relugolix while the effect on PSA is consistent with the hormone responsiveness of the patients in the HERO study. As previously noted, Study C27003 and Study C27002 were not reviewed in detail to support efficacy, however appeared consistent with the results from the HERO study.

Subpopulations

Data:

No pooling of data across studies was performed for the efficacy analyses due to differences in the definition of the primary endpoints and the much smaller study size of the phase 2 studies, relative to the phase 3 study.

The Applicant's Position:

Assessment of efficacy based on subpopulations was only evaluated in the pivotal phase 3 study (presented in Section 8.1.1). These analyses demonstrated the consistency of results across subgroups.

The FDA's Assessment:

The FDA agrees that there was consistency of castration rate across the pre-specified subgroups in HERO.

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable.

8.1.7. Integrated Assessment of Effectiveness

Data:

The primary study to support this marketing application for relugolix for the treatment of patients with advanced prostate cancer is the large prospective, randomized pivotal phase 3 study MVT-601-3201 with an active comparator, leuprolide. Supportive studies in patients with prostate cancer are the phase 2 study C27003, the phase 2 dose-finding study C27002, and the phase 1 dose-ranging study TB-AK160108.

In summary of the data presented in Section 8, relugolix 120 mg once daily:

- Achieved and sustained testosterone concentrations at castrate levels (< 50 ng/dL) for up to 48 weeks;
- More effectively reduced and maintained testosterone concentrations to castrate levels compared with leuprolide;
- Reduced testosterone rapidly without hormonal or clinical flare;
- Achieved profound castration (levels < 20 ng/dL) more rapidly and maintained sustained profound castration in more patients compared with leuprolide;
- Reduced PSA concentrations more rapidly than leuprolide, consistent with the changes observed in testosterone;
- Decreased FSH concentrations more profoundly and more rapidly than leuprolide;
- Demonstrated a more rapid testosterone recovery following treatment discontinuation unlike depot injections.

Time Course of Effect

Across studies, and in line with its mechanism of action and pharmacokinetic properties (ie, GnRH receptor antagonist with an effective half-life of 25 hours), relugolix rapidly suppresses FSH and LH concentrations (within hours) and consequently testosterone

levels (the majority of patients suppressed to castrate levels by Day 4). After treatment discontinuation, mean testosterone concentrations recover to within normal levels within 90 days.

Persistence of Efficacy

In all studies, testosterone suppression was maintained over time, and the effect persisted over the study treatment period (ie, 48 weeks in the pivotal phase 3 study and up to 96 weeks in study C27002).

The Applicant Position:

The primary objective of the development program was to demonstrate that relugolix 120 mg once daily (after a loading dose of 360 mg on Day 1) could achieve and maintain testosterone suppression to castrate levels over the required 48-week treatment duration. This was successfully demonstrated in the pivotal phase 3 study MVT-601-3201 in which the lower bound of the 95% CI for the proportion of patients with testosterone concentrations at castrate levels by Day 29 through 48 weeks was 96.7% (95% CI: 94.9%, 97.9%) exceeded the threshold of 90% established by the FDA and prespecified in the SAP. The robustness of this outcome was supported by consistent results in multiple sensitivity analyses and subgroup analyses. These findings demonstrated consistent results across a broad and diverse population of patients with advanced prostate cancer. More than 90% of patients in both groups completed the 48-week treatment period, and compliance with study drug administration, study visits and the protocol overall were high. The patients enrolled into the pivotal phase 3 study are considered representative of those in the intended labeled patient population.

In the analysis of the first key secondary endpoint, the between-group difference in sustained castration rate was 7.9% (95% CI: 4.1%, 11.8%) demonstrating superiority and noninferiority of relugolix to leuprolide. Furthermore, the hazard ratio comparing relugolix with leuprolide for risk of testosterone escape was 0.26 (95% CI: 0.15, 0.46), indicating relugolix significantly reduced the risk of testosterone escape by 74%.

This endpoint (testosterone suppression to castrate levels) is important because it directly compares the effectiveness of oral relugolix with the most commonly used ADT in clinical practice, leuprolide. The analysis was conducted in a manner consistent with the guidance for industry on the conduct of noninferiority clinical trials to establish effectiveness (FDA 2016).

Consistent with its mechanism of action, relugolix was able to more rapidly lower testosterone to castrate levels compared with leuprolide (median time to castration of 4 days vs. 27 days). Relugolix exerts a direct and rapid blockade of the GnRH receptors in the anterior pituitary, decreasing LH concentrations, avoiding the initial testosterone surge and immediately initiating reduction of testosterone concentrations. The testosterone surge that occurs with GnRH agonists may result in disease flare with reports of increased bone pain, pathologic fractures, spinal cord compression, and

bladder outlet obstruction (Oh et al. 2010). Treatment with relugolix avoids these potential safety risks, and therefore, the need for use of another medication to protect against the potential clinical flare. The most commonly used antiandrogen in combination with GnRH receptor agonists to prevent flare is bicalutamide, which has been associated with hepatotoxicity and gynecomastia (Casodex USPI 2017). While degarelix is a currently approved GnRH receptor antagonist that also results in rapid reduction in testosterone concentrations, monthly injections with an injection site reaction rate of 35% (Firmagon Prescribing Information 2020) have limited its clinical use.

The rapid suppression of testosterone also may allow the earlier initiation of concomitant therapies, like radiation therapy, which should be initiated after castrate levels of testosterone have been achieved. Literature has suggested that the cytotoxic effects of ADT and radiation are strongly co-dependent and synergistic (Siddiqui and Krauss 2018). The timing of ADT with radiation has critical implications, specifically, that starting ADT prior to radiation (neoadjuvant ADT) achieves higher efficacy than starting ADT during or after radiation (adjuvant ADT) (Zietman et al. 1997; Kaminski et al. 2003).

In addition to rapidly achieving castrate levels, the relugolix group also achieved profound castration faster than the leuprolide group. With the advent of more sensitive testosterone assays, studies have demonstrated that the goal of medical testosterone suppression should target concentrations of < 20 ng/dL, equivalent to those attained with bilateral orchiectomy (Schulman et al. 2010). Studies have also demonstrated that patients who were suppressed to the profound castrate level had a higher mean survival (Morote et al. 2007), with improved time to castration and cancer-specific survival compared with patients who did not achieve the same degree of castration (Klotz et al. 2008).

For patients with prostate cancer undergoing ADT, changes in PSA concentrations are an important indicator of the patient's response to ADT (Sasaki and Sugimura 2018). Consistent with the rapid suppression of testosterone, relugolix was able to more rapidly reduce serum PSA concentrations than leuprolide.

Levels of FSH in the relugolix group decreased rapidly coincident with a decrease in testosterone and LH levels and remained depressed to a greater degree than FSH levels in the leuprolide group, for the duration of treatment. There is a growing body of clinical and preclinical evidence showing the functional role of FSH in genitourinary malignancies, including its role in angiogenesis in pathologic microenvironments, an FSH/FSH receptor autocrine loop that may stimulate the transition from hormone-sensitive to hormone-resistant state, and the tumorigenic potential of these molecules (Hurkadli et al. 1990; Garde et al. 1991; Ben-josef et al. 1999; Mariani et al. 2006; Ide et al. 2008, 2013; Hoare et al. 2015). Although clinical studies have been retrospective in nature, a deeper degree of FSH suppression may lead to improved outcomes for patients with advanced prostate cancer, such as a longer time to castration resistance.

Unlike other ADTs (all depot injectables), relugolix, an oral non-peptide GnRH receptor antagonist, has the unique advantage of a more rapid testosterone recovery after discontinuation of treatment. Testosterone recovery was also observed in more patients 12 weeks after treatment discontinuation of relugolix than with degarelix in study C27003.

The clinical implications of testosterone recovery to normal levels within 90 days with relugolix may be significant for patients in the clinical setting. Patients with castrate levels of testosterone after discontinuation of therapy continue to be at risk of reduction in overall health and quality of life (Nascimento et al. 2019). Intermittent ADT is increasingly used for patients with prostate cancer as studies have shown improved quality of life outcomes with noninferior overall survival compared with continuous therapy (Crook et al. 2012). Patients with impending or serious health complications (eg, myocardial infarction, hip fracture, stroke) also may benefit from discontinuation of the therapy and a return of the anabolic effect of normal testosterone levels.

Androgen deprivation therapy with radiotherapy is established as an appropriate and effective treatment option for most men with newly diagnosed intermediate- and high-risk prostate cancer (Boustead and Edwards 2007). Both the European and American clinical practice guidelines suggest that 4 to 6 months of ADT may be sufficient for patients with intermediate-risk disease, whereas patients with high-risk advanced, localized disease are more likely to benefit from prolonged neoadjuvant/adjuvant ADT (18 to 36 months) with radiotherapy (Parker et al. 2015; Mottet et al. 2017; Bekelman et al. 2018; Sanda et al. 2018; Mohler and Antonarakis 2019). Meta-analyses have shown benefit from both short and long courses of ADT (Bria et al. 2009; Schmidt-Hansen et al. 2014). Consistent with the results from the study MVT-601-3201, study C27003 in patients with intermediate-risk, localized prostate cancer requiring 6 months of neoadjuvant/adjuvant relugolix to EBRT resulted in a 95% rate of sustained castration, rapid reduction in testosterone, and PSA and a complete suppression of LH and FSH.

Androgen deprivation therapy is the foundational treatment for advanced prostate cancer either as monotherapy or in combination with additional therapies, such as radiotherapy or antineoplastic therapies, for patients with significant risk of progressive disease and/or death. The benefits of relugolix demonstrated in the pivotal phase 3 study MVT-601-3201 and supported by the overall clinical development program include rapid and sustained testosterone suppression to castrate levels, an increase in the number of patients achieving and sustaining profound castration levels, and more rapid testosterone recovery following discontinuation of treatment.

The FDA's Assessment:

The substantial evidence of efficacy for this application is from the HERO study, a multinational, randomized, open-label, parallel-group study in patients with advanced androgen-sensitive prostate cancer who required at least 1 year of continuous androgen deprivation therapy (ADT).

The primary objective of the HERO study was to demonstrate the ability of relugolix to achieve and maintain suppression of serum testosterone to castrate levels (<50 ng/dL) through 48 weeks of treatment in patients with advanced prostate cancer. HERO met its primary endpoint, demonstrating that 96.7% (95% CI 94.9, 97.9) of patients who received relugolix achieved and maintained sustained testosterone suppression below castrate levels (<50 ng/dL) from Week 5 Day 1 (Day 29) to Week 49 Day 1 (Day 337) with the lower bound of the 95% CI exceeding 90%. Meeting this endpoint is consistent with FDA guidance on substantial evidence of efficacy for GnRH agents for achieving and maintaining castration.

Secondary endpoints included evaluation of non-inferiority of relugolix compared with leuprolide, cumulative probability of testosterone suppression to <50 ng/dL prior to dosing on Week 1 Day 4 (Day 4), cumulative probability of testosterone suppression to <50 ng/dL prior to dosing on Week 3 Day 1 (Day 15), proportion of patients with PSA response at Week 3 Day 1 (Day 15) followed with confirmation at Week 5 Day 1 (Day 29), cumulative probability of testosterone suppression to <20 ng/dL prior to dosing on Week 3 Day 1 (Day 15), and mean FSH levels at Week 25 Day 1 (Day 169). The outlined secondary endpoints are considered supportive of the activity of relugolix for the proposed indication.

The Applicant's claim of non-inferiority between relugolix and leuprolide and the subsequent superiority claim for relugolix over leuprolide were found to be unacceptable. The use of a non-inferiority test in the HERO study was discussed with the sponsor during the IND phase of development prior to the study start, and it was noted that this test was not acceptable (b) (4)

In addition, different censoring rules have been used in historical studies and the current HERO study, and this can affect the outcome estimates. With these issues, the constancy assumption (i.e. the similarity of the new non-inferiority trial to the historical trials) may not be valid. Thus, FDA considers these analyses exploratory.

8.2. Review of Safety

8.2.1. Safety Review Approach

Data

Evaluation of the safety of relugolix is primarily based on the pivotal phase 3 study MVT-601-3201 in men with advanced prostate cancer. The primary objective of the study was to demonstrate safety, tolerability, and efficacy of relugolix 120 mg administered orally once daily through 48 weeks of treatment following a single, oral 360-mg loading dose. A total of 624 patients were randomized to receive relugolix and 310 patients to leuprolide. Three additional clinical studies were conducted in men with prostate cancer and provide evidence in support of the dosing, efficacy and safety

analysis of relugolix in the treatment of men with advanced prostate cancer (see [Table 3](#)). These three additional studies include the phase 2 study C27003 in men with intermediate-risk localized disease requiring 6 months of neoadjuvant/adjuvant ADT to EBRT, the phase 2 dose-finding study C27002 in men with advanced prostate cancer, and the phase 1 dose-range-finding study (TB-AK160108) in nonmetastatic patients.

Other studies evaluating relugolix monotherapy in healthy participants, participants with renal or hepatic impairment, (b) (4) were included for the purpose of providing a broader evaluation of safety. The clinical pharmacology program consisted of 13 studies in healthy participants, the effect of intrinsic and extrinsic factors on the pharmacokinetics of relugolix, including the effects of renal and hepatic impairment and drug interactions, and the potential effect of relugolix on cardiac repolarization (thorough QT/QTc study). Further, (b) (4) clinical studies with relugolix (b) (4) provides a broader evaluation of safety, specifically liver safety.

These 23 studies (4 in men with prostate cancer, 13 in healthy participants, (b) (4) provide safety data on 2290 patients exposed to relugolix (840 men with prostate cancer, (b) (4) and 556 participants in clinical pharmacology studies).

As these studies had differences in design, patient populations, doses, duration of treatment and all had sample sizes smaller than the pivotal study MVT-601-3201, studies were not further pooled. The only exception was the pooling of study MVT-601-3201 and the dose-finding phase 2 study C27002 which were both conducted in men with advanced prostate cancer using the same daily dosing of 120 mg daily. In all studies, safety assessments included adverse events, vital signs, physical examination, clinical laboratory tests, and ECGs.

The Applicant's Position:

In accordance with FDA recommendations, the evaluation of the safety of relugolix is primarily based on the pivotal phase 3 study MVT-601-3201 in men with advanced prostate cancer. This pivotal phase 3 study provides a strong basis for evaluation of safety due to the large sample size of patients exposed to relugolix (622 patients were treated with relugolix of whom 563 patients completed the 48 week treatment) in the proposed indication and the randomized active-controlled study design that allows for a comparison of relugolix with leuprolide, the current standard of care. The SAP incorporated FDA feedback on an analysis using the Ischemic Heart Disease SMQ.

Four clinical studies were conducted in men with prostate cancer and provide evidence in support of the safety of relugolix in the treatment of men with advanced prostate cancer. The FDA agreed to the proposed pooling strategy to include the dose-finding phase 2 study in advanced prostate cancer with the pivotal study, however, recommended that the primary safety analysis should focus on data from study MVT-

601-3201. A thorough integrated analysis of safety was conducted across the 17 studies in the clinical development of relugolix 120 mg monotherapy for the treatment of patients with advanced prostate cancer including four studies in men with prostate cancer and 13 clinical pharmacology studies.

The safety of relugolix 120 mg monotherapy was adequately and appropriately assessed in the clinical development for the treatment of the intended broader population with advanced prostate cancer.

The FDA's Assessment:

The FDA evaluation of safety is primarily based on the results of the HERO study, The safety of relugolix in C27002 and C27003 was not reviewed in detail, but appeared consistent with the HERO study.

8.2.2. Review of Safety Database

Overall Exposure

Data:

The overall extent of exposure to relugolix monotherapy throughout the clinical development program (prostate cancer [120 mg daily] (b) (4) includes 2290 patients exposed to at least one dose of relugolix, of whom 976 patients were exposed to a relugolix dose of 120 mg or higher (see [Table 12](#)).

Table 14: Number of Patients Treated with Relugolix in Completed Trials

Relugolix Treatment Group	Number of Patients with ≥1 Dose	Number of Patients with ≥ 6 Months	Number of Patients with ≥ 12 Months
Any relugolix monotherapy	2290	841	543
80 mg	112	63	57
120 mg	863	709	486
160 mg	25		
180 mg	12		
360 mg	76		
Any relugolix monotherapy ≥120 mg	976	709	486

Includes all completed trials with relugolix monotherapy.

Clinical Pharmacology: 13 studies (TAK-385_106, TAK-385_1009, TAK-385-1010, TAK-385/CPH-010, C27001, C27005, MVT-601-1002, MVT-601-1003, MVT-601-1004, MVT-601-040, MVT-601-043, MVT-601-044, MVT-601-045).

Prostate Cancer: 4 studies (TB-AK160108, C27002, C27003, and MVT-601-3201).

(b) (4)

Exposure to the single loading doses was not included in this table.

Duration of exposure in days = (date of the last dose - date of the first dose) + 1.

Duration of exposure ≥24 weeks is considered as '≥ 6 months' and '≥ 48 weeks' as '≥ 12 months'.

Source: Table 8, Module 2.7.4

A total of 840 patients with prostate cancer were exposed to at least one dose of relugolix in the pivotal phase 3 study MVT-601-3201 (N = 622), the phase 2 study C27003 in the neoadjuvant/adjuvant setting (N = 65), the phase 2 dose-finding study C27002 in patients with advanced prostate cancer (N = 110), and the phase 1 dose-ranging study TB-AK160108 in patients with nonmetastatic prostate cancer (N = 43).

In the 13 clinical pharmacology studies supporting the prostate cancer indication, a total of 556 healthy adult men and women (or patients with mild or moderate hepatic impairment or moderate or severe renal impairment) received at least one dose of relugolix as single doses ranging from 20 to 360 mg (N = 404) or multiple doses of up to 160 mg once daily for 28 days or up to 180 mg once daily for 14 days (N = 152). Six of the 13 clinical pharmacology studies were drug interaction studies in which single 20- or 40-mg doses or multiple 40- or 120-mg doses of relugolix were coadministered with other potentially interacting medications.

In the pivotal phase 3 study MVT-601-3201, the proportion of patients completing 48 weeks of treatment was 90.2% (N = 563) in the relugolix group and 89.0% (N = 276) in the leuprolide group. Dose modifications were not permitted during the study. The mean (SD) duration of dose interruption was 3.7 (2.90) days in the relugolix group (N = 33) and of dose delay (> 90 days for dosing interval) was 3.0 (3.27) days in the leuprolide group (N = 79).

A summary of exposure to study drug and compliance in the study MVT-601-3201 is presented in [Table 13](#).

Relugolix

Table 15: Extent of Exposure and Compliance in Study MVT-601-3201 (Safety Population)

	Relugolix (N = 622)	Leuprolide (N = 308)	Total (N = 930)
Treatment duration (weeks) ^a			
Mean (SD)	45.86 (8.343)	46.05 (7.413)	45.92 (8.043)
Median	48.00	48.14	48.14
Min, Max	0.4, 51.4	1.1, 51.6	0.4, 51.6
Compliance ^b			
Mean (SD)	99.80 (2.078)	103.05 (54.303)	100.88 (31.300)
Median	100.00	99.70	100.00
Min, Max	77.3, 117.3	93.1, 1050.0	77.3, 1050.0

Abbreviations: CSR = clinical study report; Max = maximum; Min = minimum; N = number of patients in the treatment group; SD = standard deviation.

^a Treatment duration in weeks was calculated as (last dose date of any of the study drug – first dose date of study drug + 1)/7. For patients in leuprolide arm, treatment period ended 12 weeks after the last injection.

^b Compliance rate was calculated for relugolix arm with (number of tablets taken during the study / expected number of tablets during the study) × 100 and for leuprolide arm with [(cumulative dose administered / (treatment duration in weeks / 12)] / 22.5 mg or 11.25 mg per treatment on Day 1) × 100.

Source: Table 20, CSR MVT-601-3201.

The Applicant's Position:

The pivotal phase 3 study MVT-601-3201 provides a strong basis for evaluation of safety due to the large sample size of patients exposed to relugolix in the proposed indication and the randomized active-controlled study design that allows for a comparison of relugolix with leuprolide, the current standard of care. During this study, compliance in both treatment groups were high with 563 patients treated with relugolix at the proposed dose completing 48 weeks of treatment.

The safety database in the relugolix development program meets the requirements set forth in the ICH E1 guideline for extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the exposure in the HERO study and agrees that the study was of sufficient size with sufficient duration of exposure to determine the safety profile of relugolix for patients with advanced prostate cancer.

Relevant Characteristics of the Safety Population**Data:**

The pivotal, phase 3 study MVT-601-3201 and the phase 2 study C27003 were designed to enroll patients who were diagnosed as having advanced prostate cancer. Refer to Section 7.1 for an overview of the studies in patients with prostate cancer and Section 8.1.1 for the design of the pivotal study. Consequently, patient characteristics in

the pivotal study are representative of patients with advanced prostate cancer (see Section 8.1.2). Likewise, study C27003 was designed and the patient characteristics are representative of patient with intermediate-risk, localized disease requiring 6 months of ADT in the neo-/adjuvant setting to EBRT (see Section 8.1.3 and Section 8.1.4).

The Applicant's Position:

The safety population was primarily derived from the pivotal phase 3 pivotal study MVT-601-3201 as recommended by the FDA. The inclusion criteria were appropriately defined to ensure that patients who met the intended indication of advanced prostate cancer were enrolled. Overall, baseline demographics and disease-specific baseline characteristics were representative of the intended target population of patients with advanced prostate cancer (Crawford 1994; Yu et al. 1995; Pound et al. 1997; Moul 2000a, 2000b; Moul et al. 2002, 2004; D'Amico et al. 2003). All patients required at least one year of ADT per investigator assessment. More than 80% of patients had a baseline Gleason score of ≥ 7 . There was balanced representation of the three TNM disease stages in which ADT is required (ie, metastatic, locally advanced and localized disease) at study entry in patients.

The patient population in study C27002 was the same as in the pivotal study MVT-601-3201. In study C27003, patients with intermediate-risk localized disease who required 6 months of neoadjuvant/adjuvant ADT to EBRT were enrolled. Demographics and characteristics are representative of the intended target population and the safety assessment, appropriate for patients with advanced prostate cancer.

Men with prostate cancer have a higher baseline risk of developing cardiovascular disease (Keating et al. 2010b) compared to men without prostate cancer, and this risk has been shown to increase with the use of GnRH receptor agonists (Keating et al. 2010b; Haque et al. 2017). Since 2010, the FDA has required that the risk of cardiovascular disease be included in the safety information for GnRH receptor agonists.

In study MVT-601-3201, patients at high risk of cardiovascular events were excluded and patients with a prior history of MACE were well-balanced between the relugolix group (13.5%) and the leuprolide group (14.6%). However, the enrolled population had significant representation of cardiovascular risk factors in both treatment groups (91.6% in the relugolix group and 94.2% in the leuprolide group), relevant for the assessment of cardiovascular safety in the intended target population. The risk factors included any history of MACE, cerebrovascular or cardiovascular risk factors, and lifestyle-related risk factors.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the characteristics of the patients enrolled in the HERO study, which included patients with both recurrent localized and advanced prostate cancer. The FDA agrees that the study did not include patients at high

Relugolix

risk of cardiovascular events, which limits the applicability of the safety results to this population.

Adequacy of the Safety Database

Data:

The clinical safety data supporting this NDA are primarily derived from the large phase 3 registrational study MVT-601-3201, which enrolled 934 patients (624 patients in the relugolix group and 310 patients in the leuprolide group, of whom 622 and 308, respectively, received treatment). The proportion of patients completing 48 weeks of treatment was 90.2% (N = 563) in the relugolix group and 89.0% (N = 276) in the leuprolide group.

Supportive safety data are provided from three other studies in prostate cancer based on their relevance to the proposed dose and indication: C27003 (phase 2; N = 103; 65 treated with relugolix), C27002 (phase 2; N = 134; 110 treated with relugolix), TB-AK160108 (phase 1; N = 43; 43 treated with relugolix). Additional studies were included for purposes of providing a broader evaluation of safety. These studies include 13 clinical pharmacology studies in healthy participants (b) (4)

. The latter pool was specifically included to further assess liver safety across various doses.

The overall extent of exposure to relugolix throughout the clinical development program includes 2290 patients exposed to at least one dose of relugolix, of whom 976 patients were exposed to a relugolix dose of 120 mg or higher. A total of 841 patients were exposed to at least 6 months of treatment with relugolix, of whom 709 patients were exposed to a relugolix dose of 120 mg or higher.

The Applicant's Position:

The pivotal phase 3 study MVT-601-3201 provides a strong basis for evaluation of safety due to the large sample size of patients exposed to relugolix in the proposed indication and the randomized active-controlled study design that allows for a comparison of relugolix with leuprolide, the current standard of care. Additional studies were conducted and included to provide a broader evaluation of safety.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of the overall adequacy of the safety database, however as previously noted, the review of safety is based primarily on the results of the HERO study.

8.2.3. Adequacy of the Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The studies were conducted in accordance with applicable local/regional regulations and guidelines. The submission contains all required components of the eCTD.

The Applicant's Position:

There are no issues regarding data integrity and quality that impact the interpretation of safety results.

The FDA's Assessment:

Refer to Section 4.1 for a discussion of GCP issues at a single site, which did not meaningfully impact the overall safety results. The FDA otherwise agrees with the Applicant's position above.

Categorization of Adverse Events

Data:

The occurrence of an adverse event was evaluated by non-directive questioning of the patient at each visit and special investigations including clinical laboratory tests, physical examinations, vital signs and 12-lead ECGs during the study and 30 days after the last dose of study drug. Adverse events could also be detected when volunteered by the patient during or between visits. Adverse events were reported on eCRFs using investigator verbatim terms and subsequently coded using the MedDRA. Investigators were trained and required to assess every adverse event for meeting the definition of being serious and recording and reporting it appropriately. All adverse events and serious adverse events were coded according to MedDRA. Individual CSRs used the version of MedDRA that was current at the time of the study; MedDRA version 22.0 was used for study MVT-601-3201 and the pooled analysis population (MVT-601-3201 and C27002); version 20.0 was used for study TB-AK160108, version 19.0 was used for study C27002, and version 18.0 was used for study C27003. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 was used for studies MVT-601-3201, C27002, C27003, and TB-AK160108.

Adverse events summaries were generated for the overview of adverse events, all adverse events by MedDRA preferred term, adverse events by relationship to study drug, grade 3 or higher adverse events by preferred term, serious adverse events, adverse events leading to discontinuation of study drug, adverse events leading to dose modification, and fatal events. In addition, prespecified analyses were performed for safety parameters of interest defined in [Table 14](#). For study MVT-601-3201, these were predefined for analysis in the SAP.

Table 16: Adverse Event Categories for Safety Parameters of Interest in Study MVT-601-3201

Category	Search Criteria
Loss of bone mineral density	Osteoporosis/Osteopenia SMQ (broad) All PTs including the term “Fracture,” excluding “Tooth fracture” and “Fracture of penis”
QTc prolongation	Torsades de Pointes/QT Prolongation SMQ (broad)
Hepatic transaminase elevations	Protocol-specified ALT and/or AST $\geq 3 \times$ ULN Drug-Related Hepatic Disorders SMQ (narrow)
Carbohydrate and lipid metabolic effects	Dyslipidaemia SMQ (broad) Hyperglycemia/New Onset Diabetes Mellitus SMQ (narrow)
Adverse cardiovascular events	<u>Major Adverse Cardiovascular Events SMQ:</u> Myocardial Infarction SMQ (broad) Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ (broad) Deaths due to all causes <u>Ischemic heart disease SMQ:</u> Ischaemic Heart Disease SMQ (broad)
Vasomotor symptoms	The following PTs: hyperhidrosis, feeling hot, hot flush, night sweats, and flushing
Mood disorders	Depression and Suicide/Self-Injury SMQ (broad)
Hypersensitivity	Hypersensitivity SMQ (narrow)

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QT = QT-interval; SAP = statistical analysis plan; SMQ = standardised MedDRA Query; ULN = upper limit of normal.

Source: Table 9, MVT-601-3201 CSR.

To better understand the incidence of MACE, additional analyses of cardiovascular safety were conducted to provide further insight and context to the overall incidence of adverse cardiovascular events, including MACE, by treatment group. These analyses included MACE incidence by MACE medical history status, calculation of odds ratios to characterize the change in MACE risk within and between treatment groups, MACE rates derived from Kaplan-Meier methods and exposure-adjusted rates. Similar additional summarization was conducted for the incidence of ischemic heart disease.

To further explore carbohydrate and lipid metabolic effects on safety, additional analyses included adverse events of carbohydrate and lipid metabolic effects with and without a medical history using the Dyslipidemia SMQ and Hyperglycemia/New Onset Diabetes Mellitus SMQ.

To further explore mood disorder effects on safety, additional analyses included adverse events of mood disorders with and without a medical history using the Depression and Suicide/Self-Injury SMQ.

To further explore adverse events of second primary malignancy, additional analyses included adverse events of second primary malignancy by time to onset.

Tabulations summarizing the safety before and after the concomitant use of enzalutamide and docetaxel, both indicated for potential use in the protocol after PSA progression, were created as well as a similar summary of safety before and after the concomitant use of radiation therapy.

The Applicant's Position:

Studies supporting the clinical development of relugolix 120 mg daily for the treatment of men with advanced prostate cancer were adequately designed to protect patient safety while deliberately and appropriately collecting adverse events from patients, vital signs, physical examinations, clinical laboratory tests, and 12-lead ECGs. A consistent approach to the collection of adverse events was adopted across studies.

Persistently low testosterone levels from ADT are associated with a wide variety of adverse effects, including sexual dysfunction, bone mineral density loss, vasomotor symptoms, and the potential for carbohydrate and lipid metabolic abnormalities, cardiovascular events, QTc prolongation, mood disorders, and injection site reactions. Each of these side effects were assessed in the safety database.

Studies, visits, assessment, and data capturing were most appropriately setup to ensure a rigorous review and categorization of adverse events to assess the safety of relugolix for the intended treatment population – men with advanced prostate cancer.

The FDA's Assessment:

The FDA agrees that the design of the HERO study was sufficient to adequately capture and categorize adverse events. The FDA agrees with the adverse events of special interest defined by the Applicant. However, the FDA considered the use of the Standardized MedDRA Queries (SMQs) for major adverse cardiovascular events and ischemic heart disease, while likely sufficient to capture a broad array of cardiovascular events, to be exploratory in terms of determining the relative cardiac safety of relugolix compared to leuprolide. A claim of superior cardiac safety should be based on:

- a pre-specified endpoint with alpha control
- adjudication of cardiac events
- time-to-event analyses in the intent-to-treat population

The FDA determined that the cardiac safety of relugolix would optimally be described in labeling as the incidence of fatal and non-fatal myocardial infarction and stroke on the relugolix arm alone.

Routine Clinical Tests

Data:

All protocol-required laboratory assessments were conducted in accordance with the laboratory manual and the schedule of activities. Clinical laboratory assessments included hematology and chemistry as well as other assessments outlined in the individual studies. The NCI CTCAE Version 4.03 grading scale with numeric component was used to categorize toxicity grade for the laboratory parameters.

Vital signs, including systolic and diastolic blood pressure, heart rate, and temperature, were measured in the seated position after 5 minutes of rest.

Electrocardiograms (12-lead) were obtained at the timepoints specified in the Schedule of Activities and were read locally by a qualified physician. All abnormal ECG findings were documented by the investigator as clinically significant or not clinically significant.

When indicated by the study protocol, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdominopelvic region with contrast (except where contrast was medically contraindicated) and a bone scan were required to be obtained prior to randomization for each patient to determine the presence or absence of metastatic disease (patients with metastases in only regional lymph node[s] were considered N1 and were, therefore, stratified as nonmetastatic). The scans were read locally and did not need to be repeated if a scan was obtained within 60 days prior to the Baseline Day 1 visit and was available for review. However, if CT or MRI demonstrated presence of metastatic disease, a bone scan was not required. If metastatic disease was not present on CT or MRI, then a bone scan was also required.

Patients had weight and height measured during screening (within 28 days of first dose of study drug). Weight was obtained at additional timepoints as specified in the Schedule of Activities. Body mass index was calculated programmatically.

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

In phase 2 studies C27002 and C27003, slit lamp examinations and comprehensive ophthalmology evaluations were performed as a part of monitoring for phospholipidosis and similar results were observed in both the relugolix and degarelix groups. Given the lack of findings regarding phospholipidosis, which also included biomarker studies, in both phase 2 studies, the phase 3 study monitored visual acuity as an extension of the physical examination. Presenting visual acuity was assessed by the investigators with the supplied study eye chart. Patients whose presenting visual acuity score was 90 or lower at the screening visit were encouraged to obtain a diagnostic evaluation from an eye care provider (ie, an ophthalmologist or optometrist). Any findings (ie, diagnoses) from the eye examination were recorded as medical history. Patients whose presenting visual acuity score during the study had decreased by ten or more points from baseline

were referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation had to be submitted to the sponsor.

The Applicant's Position:

The routine clinical tests used in the clinical development of relugolix for the treatment of advanced prostate cancer are standard recognized measures for this type of clinical study. All laboratory assays had to be conducted in accordance with the laboratory manual and the schedule of activities. The approach to clinical tests was consistent across studies.

The safety parameter of interest, hepatic transaminase elevations, was assessed by reviewing protocol-specified reporting of adverse events of clinical interest (ALT and/or AST $\geq 3 \times$ upper limit of normal [ULN]) as reported in central clinical laboratory data and on the Adverse Event eCRF. Hepatic transaminase elevations were monitored closely in accordance with FDA drug-induced liver injury guidelines (FDA 2009).

The routine clinical tests and data captured were appropriately established and validated to ensure a rigorous assessment of the safety of relugolix for the intended broader population of men with advanced prostate cancer.

The described approach for assessment of routine clinical tests was sufficient to assess the safety of relugolix for the intended treatment population.

The FDA's Assessment:

The FDA agrees that safety monitoring in the HERO study was sufficient to adequately describe the safety profile of relugolix in patients with advanced prostate cancer.

8.2.4. Safety Results

Deaths

Data:

A summary of treatment-emergent adverse events that led to fatal outcomes in study MVT-601-3201 is presented in [Table 15](#).

Table 17: Adverse Events Resulting in Fatal Outcome in Study MVT-601-3201 (Safety Population)

Preferred Term	Relugolix (N = 622)	Leuprolide (N = 308)
Patients with at least one AE resulting in fatal outcome, n (%)	7 (1.1%)	9 (2.9%)
Acute kidney injury	1 (0.2%)	0
Acute myocardial infarction	1 (0.2%)	0
Myocardial infarction	1 (0.2%)	0
Non-small cell lung cancer metastatic	1 (0.2%)	0
Prostate cancer	1 (0.2%)	0
Prostate cancer metastatic	1 (0.2%)	2 (0.6%)

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Preferred Term	Relugolix (N = 622)	Leuprolide (N = 308)
Small cell lung cancer metastatic	1 (0.2%)	0
Aortic stenosis	0	1 (0.3%)
Cardiac failure congestive	0	1 (0.3%)
Cardio-respiratory arrest	0	3 (1.0%)
Cardiopulmonary failure	0	1 (0.3%)
Cerebral haemorrhage	0	1 (0.3%)
Epistaxis	0	1 (0.3%)
Homicide	0	1 (0.3%)
Multiple organ dysfunction syndrome	0	1 (0.3%)

Abbreviations: AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the treatment group; n = number of patients with specified AE.

Patients with multiple events for a given preferred term are counted only once for each preferred term.

Events are sorted by decreasing frequency of preferred term in the relugolix group.

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Patient (b) (6) (relugolix) had a fatal non-treatment-emergent adverse event (general physical health deterioration) (Listing 16.2.7.3, CSR MVT-601-3201), reported after completion of the protocol-specified safety reporting period and is not included in this table.

Source: Table 38, CSR MVT-601-3201.

All adverse events that led to a fatal outcome were assessed by the investigator as not related to study drug, except for one patient in the relugolix group with an event of acute myocardial infarction.

During the final weeks prior to database lock, sites attempted to contact all study participants or their immediate family regarding the survival status of previously enrolled/completed study patients. If the site was unsuccessful in contacting the patient and/or immediate family, the site may have accessed hospital records or publicly available sources such as national registries, newspaper obituaries, and social networking websites. There were eight patients whose survival status was unknown. There were four patients in the relugolix group with deaths reported on the health status survey. Two patients discontinued early in the study (ie, Day 2 and Day 45) and died on Day 463 and Day 663, respectively. The other two patients completed the 48 weeks of treatment; one died of prostate cancer progression on Day 511 and the other died of unknown cause on Day 449. One patient in the leuprolide group died from prostate cancer progression on Day 330 after discontinuing on Day 169.

In study C27002, five deaths were reported: four in the relugolix dose groups (two each) and one in the leuprorelin group. None of the fatal events were considered related to study treatment. In the relugolix 80-mg group, one patient died from cerebral hemorrhage and one from cardiac arrest. In the relugolix 120-mg group, one patient had sudden death and one died of natural cause. In the leuprorelin group, one patient died due to myocardial infarction. Given the randomization ratio (relugolix 80 mg, relugolix 120 mg, leuprorelin; 2:2:1) in this study, the incidence of adverse events with fatal outcome was similar across the three groups.

No deaths were reported in the supportive studies (C27003 or TB-AK160108), in studies of patients with hepatic or renal impairment, in phase 1 studies of healthy participants, or in studies in women's health indications.

The Applicant's Position:

Despite similar proportions of patients with cardiovascular risk factors at baseline, there were fewer cardiovascular-related fatal events in the relugolix group than in the leuprolide group in study MVT-601-3201.

The FDA's Assessment:

The FDA agrees with the Applicant's presentation of deaths in the HERO study. Excluding death due to prostate cancer, deaths related to adverse events were uncommon and of similar incidence on both the relugolix and leuprolide arms.

Serious Adverse Events

Data:

A summary of serious adverse events reported for $\geq 0.5\%$ of patients by preferred term in study MVT-601-3201 is presented in [Table 16](#).

Relugolix

Table 18: Serious Adverse Events Reported for $\geq 0.5\%$ of Patients in Either Treatment Group by Preferred Term in Study MVT-601-3201 (Safety Population)

Preferred Term	Relugolix (N = 622)	Leuprolide (N = 308)
Patients with at least one serious AE, n (%)	76 (12.2%)	47 (15.3%)
Acute myocardial infarction	5 (0.8%)	1 (0.3%)
Acute kidney injury	4 (0.6%)	1 (0.3%)
Urinary tract infection	3 (0.5%)	2 (0.6%)
Prostate cancer metastatic	2 (0.3%)	2 (0.6%)
Anaemia	0	3 (1.0%)
Cardio-respiratory arrest	0	3 (1.0%)
Cerebral haemorrhage	0	2 (0.6%)
Inguinal hernia	0	2 (0.6%)
Presyncope	0	2 (0.6%)
Syncope	0	2 (0.6%)
Transient ischaemic attack	0	3 (1.0%)

Abbreviations: AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the treatment group; n = number of patients with specified AE.

Patients with multiple events for a given preferred term are counted only once for each preferred term.

Events are sorted by decreasing frequency of preferred term in the relugolix group.

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Source: Table 40, CSR MVT-601-3201.

Eighty-one patients (8.7%) had a grade 3 serious adverse event, with proportions similar between the two groups (8.0% in the relugolix group and 10.1% in the leuprolide group).

Six patients (1.0%) in the relugolix group had a grade 4 serious adverse event: endocarditis and septic shock (both in a single patient), acute myocardial infarction, myocardial infarction, ischemic stroke, suicidal ideation, and chronic kidney disease. Two patients (0.6%) in the leuprolide group had a grade 4 serious adverse event: liver function test abnormal in one patient and pulmonary edema and rhabdomyolysis in another patient.

Drug-related serious adverse events were reported for six patients (1.0%) in the relugolix group and three patients (1.0%) in the leuprolide group. The preferred terms reported for the six patients in the relugolix group were gastric ulcer hemorrhage, acute myocardial infarction, hip fracture, acute left ventricular failure and aortic stenosis (both in a single patient), acute coronary syndrome and cellulitis (both in a single patient), and cardiac failure congestive and chronic kidney disease (both in a single patient). The preferred terms reported for the three patients in the leuprolide group were cardiac failure, sinus node dysfunction, and hyperglycemia and transient ischemic attack (both in a single patient). No drug-related serious adverse event was reported for more than one patient.

In study C27003, serious adverse events were reported for 2% of patients in the relugolix group compared with 8% of patients in the degarelix group. Serious adverse events in the pooled analysis population (MVT-601-3201 and C27002) were consistent with the pivotal study.

The Applicant's Position:

The incidence of serious adverse events was lower in the relugolix group (12.2%) compared to the leuprolide group (15.3%) with no important imbalances except for MACE which is discussed in the Safety Parameters of Clinical Interest section. The proportion of serious adverse events of grade 3 or higher were similar between the two groups. Drug-related serious adverse events were reported for the same proportion of patients in both groups (1.0%).

The types of serious adverse events observed are consistent with the population of patients with advanced prostate cancer and age-related comorbidities, with no imbalance observed in patients treated with relugolix.

The FDA's Assessment:

The FDA agrees with the Applicant's presentation of SAEs in HERO above. Excluding events due to prostate cancer, 12% of patients receiving relugolix experienced SAEs. Serious adverse reactions in $\geq 0.5\%$ of patients included myocardial infarction (0.8%), acute kidney injury (0.6%), arrhythmia (0.6%), hemorrhage (0.6%), and urinary tract infection (0.5%). Overall, the incidence and categorization of SAEs was similar between the relugolix and leuprolide arms.

Dropouts and/or Discontinuation Due to Adverse Events

Data:

A summary of adverse events that led to study drug withdrawal by decreasing frequency of preferred term in study MVT-601-3201 is provided in [Table 17](#).

Table 19: Adverse Events Leading to Study Drug Withdrawal by Preferred Term in Study MVT-601-3201 (Safety Population)

Preferred Term	Relugolix (N = 622)	Leuprolide (N = 308)
Patients with at least one AE leading to study drug withdrawal, n (%)	22 (3.5%)	1 (0.3%)
Atrioventricular block second degree	2 (0.3%)	0
Abdominal pain	1 (0.2%)	0
Abdominal pain upper	1 (0.2%)	0
Acute kidney injury	1 (0.2%)	0
Adenocarcinoma of colon	1 (0.2%)	0
Alanine aminotransferase increased	1 (0.2%)	0

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Relugolix

Preferred Term	Relugolix (N = 622)	Leuprolide (N = 308)
Anaemia	1 (0.2%)	0
Anosmia	1 (0.2%)	0
Atrial fibrillation	1 (0.2%)	0
Cardiac failure	1 (0.2%)	0
Cardiac failure congestive	1 (0.2%)	0
Chronic kidney disease	1 (0.2%)	0
Cognitive disorder	1 (0.2%)	0
Constipation	1 (0.2%)	0
Delirium	1 (0.2%)	0
Dyspnoea	1 (0.2%)	0
Electrocardiogram QT prolonged	1 (0.2%)	0
Endocarditis	1 (0.2%)	0
Fall	1 (0.2%)	0
Fatigue	1 (0.2%)	0
Gastric ulcer haemorrhage	1 (0.2%)	0
Haemorrhagic stroke	1 (0.2%)	0
Hepatic enzyme increased	1 (0.2%)	0
Hot flush	1 (0.2%)	0
Hypertension	1 (0.2%)	0
Hypokalaemia	1 (0.2%)	0
Hyponatraemia	1 (0.2%)	0
Insomnia	1 (0.2%)	0
Lacunar infarction	1 (0.2%)	0
Loss of libido	1 (0.2%)	0
Muscular weakness	1 (0.2%)	0
Parosmia	1 (0.2%)	0
Pneumonia	1 (0.2%)	0
Pneumonia aspiration	1 (0.2%)	0
Prostate cancer	1 (0.2%)	0
Septic shock	1 (0.2%)	0
Small cell lung cancer metastatic	1 (0.2%)	0
Taste disorder	1 (0.2%)	0
Weight decreased	1 (0.2%)	0
Weight increased	1 (0.2%)	0
Dysphagia	0	1 (0.3%)
Haemorrhage intracranial	0	1 (0.3%)

Abbreviations: AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the treatment group; n = number of patients with specified AE.

Patients with multiple events for a given preferred term are counted only once for each preferred term.

Events are sorted by decreasing frequency of preferred term in the relugolix group.

Adverse events with action taken of study drug withdrawn are taken from the AE case report form.

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Source: Table 41, CSR MVT-601-3201.

Adverse events that led to study drug withdrawal were reported for 22 patients (3.5%) in the relugolix group and one patient (0.3%) in the leuprolide group.

Relugolix

Atrioventricular block second degree (in two patients in the relugolix group and no patient in the leuprolide group) was the only adverse event resulting in study drug withdrawal reported for more than one patient.

Adverse events that led to study drug withdrawal in the pooled analysis population (MVT-601-3201 and C27002) are consistent with those reported in study MVT-601-3201. In study C27003, no adverse event leading to study discontinuation was reported.

The Applicant's Position:

A review of adverse events leading to study drug withdrawal indicate that the relugolix safety profile in patients with advanced prostate cancer is generally consistent with that of the general population or what would be expected with GnRH analogues. The imbalance in adverse events that led to study drug withdrawal in the pivotal study is likely due to inherent differences in the reporting of action taken with a study drug given as a daily oral dose versus a 3-month depot injection. All fatal events in the leuprolide group (nine patients [2.9%]) were not captured as adverse events leading to study drug discontinuation; the incidence of adverse events that led to withdrawal of study treatment or fatal outcome was comparable between the relugolix group (3.9%) and the leuprolide group (3.2%).

No discernable pattern of events leading to study drug withdrawal was noted.

The FDA's Assessment:

The FDA agrees with the Applicant's presentation of study drug withdrawal data above. The FDA agrees that the incidence of withdrawal was higher on the relugolix arm compared to the leuprolide arm, but that the difference in administration between an oral versus depot injectable drug may confound interpretation of these data. In the relugolix arm, there was no indication of a clear pattern or trend of any particular relugolix associated toxicities that lead to withdrawal.

Dose Interruptions/Reductions Due to Adverse Effects

Data:

In study MVT-601-3201, adverse events that led to study drug interruption were reported for 17 patients (2.7%) in the relugolix group and no patients in the leuprolide group. Twenty-five patients (3.7%) in the pooled relugolix group had one or more adverse event leading to dose modification compared to no dose modifications in patients taking leuprolide. In study C27003, two patients (3%) in the relugolix group (120 mg) and none in the degarelix group were reported to have an adverse event resulting in drug dose modification; for one patient, the dose was reduced, and for the other, the dose was increased.

The Applicant's Position:

The higher proportion of patients with adverse events leading to study drug interruption in the relugolix group is likely secondary to the increased flexibility for interruption of

the treatment regimen for an orally-delivered study drug relative to the more limited options for interruption of depot injectable ADTs. Patients did not have the option to interrupt an injection unless the adverse event coincided with the date that the patient was scheduled per protocol for a repeat injection. No adverse event resulting in study drug interruption was reported for more than one patient.

The FDA's Assessment:

As noted in the discussion of drug withdrawals above, the FDA agrees that the difference in administration may confound interpretation and comparison between arms of study drug interruption.

Safety Parameters of Clinical Interest

Data:

Safety parameters of clinical interest represent prespecified categories of adverse events that are either known toxicities of ADT with GnRH receptor agonists (vasomotor symptoms, carbohydrate and lipid metabolic effects, mood disorders, adverse cardiovascular events, loss of bone mineral density, and QTc prolongation), potential risks associated with relugolix based on nonclinical data (hepatic transaminase elevations), or theoretical risks with an investigational agent (hypersensitivity). An overall summary of these adverse events categories is provided in [Table 18](#).

Table 20: Overall Summary of Adverse Event Categories Study MVT-601-3201 (Safety Population)

AE Categories	Relugolix (N = 622)	Leuprolide (N = 308)
Vasomotor symptoms	349 (56.1%)	169 (54.9%)
Carbohydrate and lipid metabolic effects	53 (8.5%)	23 (7.5%)
Hepatic transaminase elevations	47 (7.6%)	17 (5.5%)
Hypersensitivity	44 (7.1%)	26 (8.4%)
Mood disorders	32 (5.1%)	14 (4.5%)
Adverse cardiovascular events	24 (3.9%)	22 (7.1%)
Major adverse cardiovascular events	18 (2.9%)	19 (6.2%)
Ischemic heart disease	15 (2.4%)	5 (1.6%)
Loss of bone mineral density	20 (3.2%)	12 (3.9%)
QTc prolongation	13 (2.1%)	6 (1.9%)

The database lock date was 10 Dec 2019.

Abbreviations: AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the treatment group.

Patients with multiple events for a given category were counted only once for each category.

Events are sorted by decreasing frequency of categories in the relugolix group.

Each AE category was summarized based on predefined searching criteria documented in the statistical analysis plan. MedDRA Version 22.0.

Source: Table 42, CSR MVT-601-3201.

Except for vasomotor symptoms, no safety parameter of interest was reported for \geq 10% of patients in either group.

Relugolix

Fracture-related events were reported for 1.4% of patients in the relugolix group versus 1.0% of patients in the leuprolide group.

Although adverse events consistent with abnormal glucose or lipid metabolism were reported with similar frequency in both groups and mean hemoglobin A1c (HbA1c) increases over time were comparable between groups, mean fasting glucose over 48 weeks increased less in the relugolix group (+0.39 mmol/L) compared with the leuprolide group (+0.51 mmol/L). Further, the proportions of patients with fasting glucose concentrations meeting predefined limits of change were also lower in the relugolix group compared with the leuprolide group (eg, glucose \geq 200 mg/dL and $>$ than baseline in 7.4% relugolix, 13.0% leuprolide).

All other safety parameters of interest (ie, hypersensitivity, mood disorders, QTc prolongation) were reported in similar proportions of patients for both groups. The most common hypersensitivity-related adverse events were rash (3.2% of patients in the relugolix group and 2.3% in the leuprolide group), followed by eczema (1.4% and 1.3%, respectively), and urticaria (1.1% and 1.3%, respectively). Depression was the most commonly reported mood disorder-related adverse event (reported in 1.9% of patients in the relugolix group and 1.0% in the leuprolide group) followed by memory impairment (1.1% and 1.0%, respectively), and mood swings (0.6% and 1.3%, respectively). Syncope was the most commonly reported adverse event potentially associated with QTc prolongation (reported in 1.3% of patients in the relugolix group and 1.0% in the leuprolide group).

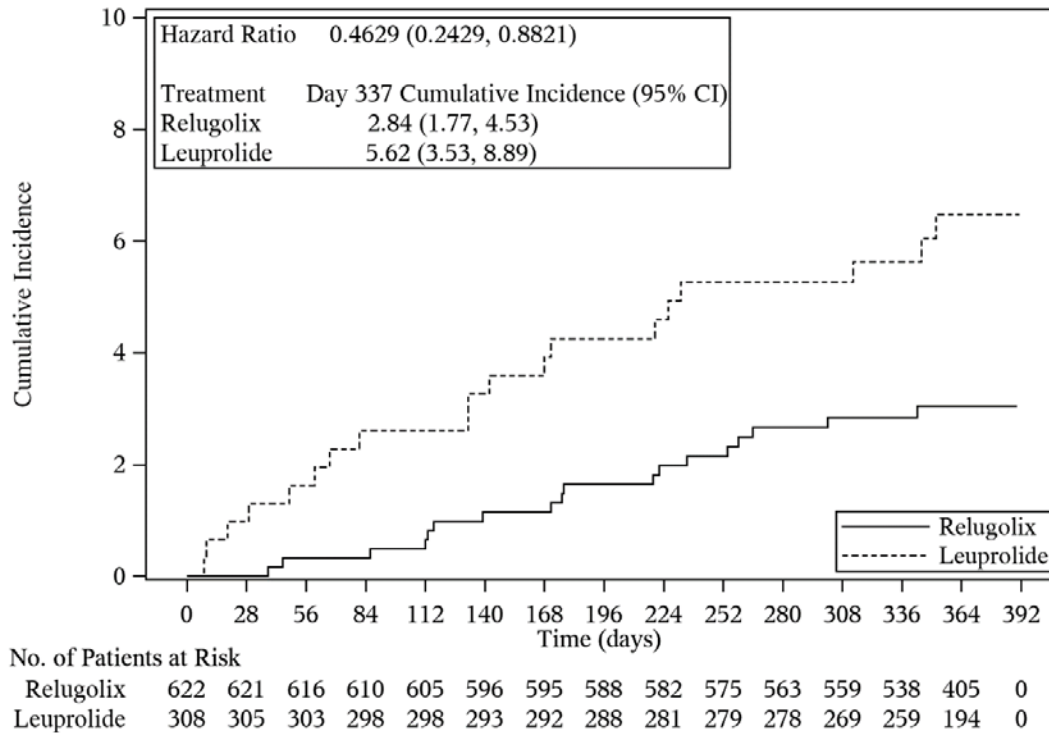
Major Adverse Cardiovascular Events

In the pivotal phase 3 study MVT-601-3201 in men with advanced prostate cancer, adverse events consistent with MACE were reported over 48 weeks of ADT for 2.9% of patients in the relugolix group compared with 6.2% of patients in the leuprolide group.

An exploration of the incidence of MACE events in patients with or without a reported medical history of adverse cardiovascular events was performed, applying the MACE query to the medical history data to identify medical history events. In the subgroup of patients with a reported medical history of MACE, the percentage of patients with at least one adverse event associated with MACE while on study drug treatment was lower in the relugolix group (3.6%) than the leuprolide group (17.8%), reflecting a 5.8-fold higher odds of having an event in men treated with leuprolide compared with relugolix. In patients without a reported medical history of MACE, the percentage of patients with at least one adverse event associated with MACE while on study drug treatment was lower in the relugolix group (2.8%) than the leuprolide group (4.2%).

The cumulative incidence of MACE in all patients is shown in [Figure 14](#).

Figure 15: Cumulative Incidence of Major Adverse Cardiovascular Events (Safety Population)



The database lock date was 10 Dec 2019.
Abbreviations: CI = confidence interval.
Source: Figure 12, Module 2.5.

The Kaplan-Meier curves for time to event separated within the first 4 weeks of the study and continued to separate through the safety follow up visit. After 48 weeks of treatment, the estimates of MACE rate continued to be lower in the relugolix group at 2.84% (95% CI: 1.77%, 4.53%) compared with the leuprolide group at 5.62% (95% CI: 3.53%, 8.89%). This demonstrates a 54% reduction in risk of MACE in the relugolix group compared with leuprolide (HR = 0.4629; 95% CI: 0.2429, 0.8821).

The results of all analyses of adverse cardiovascular events as defined above for study MVT-601-3201 are comparable to those presented in the pooled population as the pooled population only contains three additional events. These include one event in the relugolix group (embolic stroke) and two events in the leuprolide group (myocardial infarction and transient ischemic attack). In study C27003, 2/65 patients (3.1%) in the relugolix 120 mg group had MACE (retinal artery occlusion, troponin I increased) compared with no patients in the degarelix group.

Hepatic Transaminase

In study MVT-601-3201, there were 13 patients (9 [1.4%] in the relugolix group and 4 [1.3%] in the leuprolide group) with an adverse event of clinical interest (ALT and/or AST $\geq 3 \times$ ULN) reported during the study, with a similar proportion of patients in both groups. Of these patients, 10 patients (six in the relugolix group and four in the leuprolide group) had ALT $\geq 3 \times$ ULN.

Mean changes in ALT and AST over time in the relugolix and leuprolide groups were similar. The proportions of patients with laboratory values meeting predefined limits of change at any time for ALT or AST were also similar in both treatment groups (see Laboratory Findings section).

Overall, hepatic safety adverse events, as identified by the Drug-related hepatic disorders MedDRA SMQ (narrow), were reported for a higher proportion of patients in the relugolix group (7.6%) than in the leuprolide group (5.5%). The most frequently reported adverse events of hepatic transaminase elevations were ALT increased and AST increased; both terms were reported for a higher proportion of patients in the relugolix group (4.2% and 2.7%, respectively) compared with the leuprolide group (2.6% and 1.3%, respectively). Events of hepatic function abnormal (three patients [0.5%]), liver disorder (two patients [0.3%]) and transaminases increased (two patients [0.3%]) were reported for more than one patient in the relugolix group compared with no patients in the leuprolide group.

One serious adverse event of grade 4 liver function test abnormal was reported for a patient with widely metastatic disease in the leuprolide group (pulmonary, hepatic, pancreatic, and splenic lesions, all suspicious for metastasis); no action was taken with study drug leuprolide. One patient discontinued study drug due to ALT increased.

The proportion of patients with adverse events in the Drug-related hepatic disorders SMQ (narrow) were comparable to the single pivotal study data (7.5% vs. 6.3%, a difference of 1.2%). The differences between groups in the incidences of the ALT increased and AST increased were less in the pooled analysis (difference of $< 1\%$ between groups) than in study MVT-601-3201 (difference of approximately 1.5% between groups). No additional adverse events pertaining to hepatic disorders met criteria for seriousness for patients in the relugolix group.

In study C27003, no hepatic adverse events, as identified by the Drug-related hepatic disorders MedDRA SMQ (narrow), were reported in the relugolix group. By contrast, in the degarelix group, 5 patients (13%) were reported to have adverse events of ALT increased and 2 patients (5%) were reported to have adverse events of AST increased.

The Applicant's Position:

Major Adverse Cardiovascular Events

Men with prostate cancer have a higher baseline risk of developing cardiovascular disease (Keating et al. 2010b) compared to men without prostate cancer, and this risk

has been shown to increase with the use of GnRH receptor agonists (Keating et al. 2010b; Haque et al. 2017). In study MVT-601-3201, the incidence of MACE after 48 weeks of ADT was lower in the relugolix group (2.9%) compared with the leuprolide group (6.2%), a 54% risk reduction (HR = 0.46, 95% CI: 0.24, 0.88).

The early cardiovascular risk associated with GnRH receptor agonist treatment in men with pre-existing cardiovascular disease was reported by Albertsen et al. (2014) after conducting a large meta-analysis of 2328 men, designed to compare the efficacy of GnRH receptor agonists against the GnRH receptor antagonist degarelix. Among men with pre-existing cardiovascular disease, the risk of cardiac events within 1 year of initiating therapy was significantly lower among men treated with a GnRH receptor antagonist compared with GnRH receptor agonists (HR: 0.44; [95% CI: 0.26, 0.74], $p = 0.0002$) (Albertsen et al. 2014).

A similar finding was also reported in a small prospective randomized phase 2 study comparing leuprolide to degarelix. Of the 80 patients with prostate cancer and pre-existing cardiovascular disease randomized to the GnRH receptor agonist, 20% experienced a major cardiovascular or cerebrovascular event compared with 3% of those randomized to GnRH receptor antagonist treatment ($p = 0.013$), with an absolute risk reduction in major cardiovascular and cerebrovascular events at 12 months of 18.1% (95% CI: 4.6, 31.2; $p = 0.032$) (Margel et al. 2019). These findings are consistent with evidence presented in multiple observational studies and retrospective studies comparing GnRH receptor agonists to GnRH receptor antagonists or no ADT (Keating et al. 2006; Saigal et al. 2007; Zhao et al. 2014; Bosco et al. 2015).

Relugolix is the first GnRH receptor antagonist to demonstrate a reduced risk of MACE compared to leuprolide in a large, prospective, randomized phase 3 clinical trial, MVT-601-3201. Given the study's exclusion criteria, patients with a medical history of MACE comprised a smaller and similar proportion of patients in both treatment groups (13.5% in the relugolix group vs. 14.6% in the leuprolide group) than the reported prevalence of approximately 30% in a non-selected population of patients with advanced prostate cancer (Albertsen et al. 2014; Davis et al. 2015). The enrolled population, however, had significant representation of cardiovascular risk factors in both treatment groups (91.6% in the relugolix group and 94.2% in the leuprolide group). The risk factors included any history of MACE, cerebrovascular or cardiovascular risk factors, and lifestyle-related risk factors.

This prespecified analysis was performed for safety and therefore was not an alpha-protected endpoint in the study, and no adjustments were made for multiplicity of testing. However, the magnitude of the differences observed and the rigor and completeness of adverse event collection in this study mitigate the likelihood of these differences having occurred by chance in this large randomized prospective trial with comparable cardiovascular history and risk factors at baseline. The study used the Standardised MedDRA Query for MACE as agreed with the Agency. The MACE events were not adjudicated, however, the reported events and patient narratives provided are

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consistent with those events recommended to be included by the 2017 Cardiovascular and Stroke Endpoint Definitions publication developed by the Standardized Data Collection for Cardiovascular Trials Initiative and FDA (Hicks et al. 2018).

In summary, relugolix was associated with a reduced risk of major adverse cardiovascular events compared with leuprolide in a prespecified safety analysis of a prospective randomized phase 3 clinical trial. These results demonstrate a potential clinically meaningful benefit in safety over leuprolide, the standard of care ADT.

Hepatic Transaminase

Hepatic transaminase elevations (asymptomatic, predominantly grade ≤ 2 and transient) have been reported for $< 1\%$ of participants in relugolix program studies; such transient serum transaminase elevations have been noted with other GnRH analogues.

There were more adverse events identified per the Drug-related hepatic disorders – comprehensive search SMQ (narrow) in the relugolix group (7.6%) compared to the leuprolide group (5.5%) in study MVT-601-3201; specifically, adverse events of ALT increased were reported for 4.2% in the relugolix group and 2.6% in the leuprolide group. However, mean ALT and AST concentrations over time were similar in both treatment groups.

The incidence of adverse events of clinical interest (ALT and/or AST $\geq 3 \times$ ULN) was also comparable between patients treated with relugolix (1.4%) and leuprolide (1.3%). No evidence of drug-induced liver injury was observed. Increased ALT is considered an adverse drug reaction.

The effect of relugolix on glucose metabolism appears to be less than that observed with leuprolide acetate, particularly in patients with inadequate glycemic control at baseline, although patients were not stratified at baseline for risk factors for abnormal glucose metabolism.

Other known toxicities of ADT (ie, loss of bone mineral density, QTc prolongation, mood disorders, and vasomotor symptoms, and hypersensitivity) were reported in similar proportions of patients for both groups. Labelling provides for appropriate guidance.

The FDA's Assessment:

The FDA agrees with the Applicant's presentation of events of vasomotor symptoms, mood disorders, loss of bone mineral density, metabolic events of dyslipidemia and hyperglycemia, and QTc prolongation, which were similar in incidence between the relugolix and leuprolide arms of HERO and are consistent with class effects for androgen deprivation therapy. Additionally, there was no increased risk for hypersensitivity events for relugolix compared to leuprolide, and all events were of low grade.

The FDA agrees that there was an increase in all-grade hepatic transaminase elevation events in the relugolix compared to the leuprolide arm, however there was no meaningful difference between the two arms when considering laboratory elevations of

Relugolix

ALT worsening from baseline (all-grade ALT increase: 27% vs 28% and Grade 3-4 increase: 0.3% vs 0% for relugolix and leuprolide respectively). No patients discontinued relugolix due to hepatic toxicity.

The FDA does not agree that the HERO study demonstrated an improved cardiac safety profile compared to leuprolide. While the incidence of MACE as defined by the SMQs of myocardial infarction, central nervous system hemorrhages, and cerebrovascular conditions, and death due to any cause was numerically lower on the relugolix arm compared to the leuprolide arm, analysis of MACE was pre-specified only as a descriptive endpoint without alpha control and no adjudication was performed. The FDA considers these results exploratory only. (b) (4)

Overall, 17 patients (2.7%) on the relugolix arm experienced any event, including 8 (1.3%) Grade 3-4 events, and two fatal myocardial infarctions. In the absence of a placebo arm, the overall cardiac safety of relugolix cannot be fully assessed, however the FDA considers the cardiac safety acceptable for the indicated population.

Table 21: Cardiovascular and stroke events in the HERO study

Grouped Term	Trial arm					
	Relugolix N = 622			Leuprolide N = 308		
	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Any grouped term	17 (2.7)	8 (1.3)	2 (0.3)	4 (1.3)	1 (0.3)	0
Cardiac Disorders (GT)	17 (2.7)	8 (1.3)	2 (0.3)	4 (1.3)	1 (0.3)	0
Acute myocardial infarction	5	4	1	1	1	0
ECG signs of myocardial ischaemia	2	0	0	0	0	0
Ischaemic stroke	2	1	0	0	0	0
Myocardial infarction	2	1	1	0	0	0
Acute coronary syndrome	1	1	0	0	0	0
Angina pectoris	1	0	0	2	0	0
Electrocardiogram ST-T segment depression	1	0	0	0	0	0
Electrocardiogram ST segment elevation	1	0	0	0	0	0

Grouped Term	Trial arm					
	Relugolix N = 622			Leuprolide N = 308		
	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Haemorrhagic stroke	1	1	0	0	0	0
Lacunar infarction	1	1	0	0	0	0
Myocardial ischaemia	1	0	0	1	0	0

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, TRT01A, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN.

Note: Custom grouped terms are designated by '(GT)'.

Cardiac disorders (GT) includes: Acute coronary syndrome, Acute myocardial infarction, Angina pectoris, ECG signs of myocardial ischaemia, Electrocardiogram ST-T segment depression, Electrocardiogram ST segment elevation, Haemorrhagic stroke, Ischaemic stroke, Lacunar infarction, Myocardial infarction, and Myocardial ischaemia.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Adverse event summaries are based on treatment-emergent adverse events (hereafter, adverse events, unless otherwise specified). A treatment-emergent adverse event was defined as any adverse event with an onset following administration of the first dose of study drug.

An overall summary of adverse events in study MVT-601-3201 is presented in [Table 19](#). A summary of adverse events reported for at least 5% of patients (per preferred term) in either treatment group in study MVT-601-3201 is presented in [Table 20](#).

Table 22: Overview of Adverse Events in Study MVT-601-3201 (Safety Population)

No. of Patients with at Least One AE	Relugolix (N = 622)	Leuprolide (N = 308)
Any	578 (92.9%)	288 (93.5%)
Leading to study treatment withdrawn	22 (3.5%)	1 (0.3%)
Leading to study treatment interruption	17 (2.7%)	0
Grade ≥3	112 (18.0%)	63 (20.5%)
Grade ≥3 related to study drug	21 (3.4%)	8 (2.6%)
Related to study drug	458 (73.6%)	212 (68.8%)
Serious	76 (12.2%)	47 (15.3%)
Serious and related to study drug	6 (1.0%)	3 (1.0%)
Serious and leading to treatment discontinuation	10 (1.6%)	1 (0.3%)
Fatal outcome	7 (1.1%)	9 (2.9%)

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No. of Patients with at Least One AE	Relugolix (N = 622)	Leuprolide (N = 308)
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The database lock date was 10 Dec 2019.

Abbreviations: AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the treatment group.

AE grades were evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

Related AEs were rated by the investigators as possibly or probably related to study drug.

Patients with multiple events were counted once.

Source: Table 33, CSR MVT-601-3201.

Table 23: Summary of Adverse Events Reported for ≥ 5% of Patients in Either Treatment Group by Preferred Term in Study MVT-601-3201 (Safety Population)

Preferred Term	Relugolix (N = 622)	Leuprolide (N = 308)
No. of patients with at least one AE, n (%)	578 (92.9%)	288 (93.5%)
Hot flush	338 (54.3%)	159 (51.6%)
Fatigue	134 (21.5%)	57 (18.5%)
Constipation	76 (12.2%)	30 (9.7%)
Diarrhoea	76 (12.2%)	21 (6.8%)
Arthralgia	75 (12.1%)	28 (9.1%)
Nasopharyngitis	59 (9.5%)	29 (9.4%)
Back pain	50 (8.0%)	28 (9.1%)
Hypertension	49 (7.9%)	36 (11.7%)
Weight increased	49 (7.9%)	20 (6.5%)
Insomnia	43 (6.9%)	14 (4.5%)
Pollakiuria	37 (5.9%)	20 (6.5%)
Nausea	36 (5.8%)	13 (4.2%)
Nocturia	36 (5.8%)	19 (6.2%)
Dizziness	35 (5.6%)	17 (5.5%)
Headache	35 (5.6%)	13 (4.2%)
Pain in extremity	33 (5.3%)	19 (6.2%)
Asthenia	32 (5.1%)	21 (6.8%)
Urinary incontinence	30 (4.8%)	16 (5.2%)
Hyperhidrosis	15 (2.4%)	16 (5.2%)

The database lock date was 10 Dec 2019.

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE.

Patients with multiple events for a given preferred term are counted only once for each preferred term.

Events are sorted by decreasing frequency of preferred term in the relugolix group.

MedDRA Version 22.0.

Source: Table 34, CSR MVT-601-3201.

Adverse events were generally reported with similar frequency in both treatment groups with the exception of adverse events consistent with MACE and adverse events of constipation, diarrhea, arthralgia, and hypertension. Otherwise, observed differences between groups were usually small, favoring one treatment group or the other without a clear discernible pattern.

Adverse events of constipation, diarrhea, and arthralgia were reported with greater frequency in the relugolix group. All adverse events of constipation and diarrhea were mild or moderate (grade 1 or grade 2) in severity. No serious adverse events of constipation or diarrhea were reported. One patient in the relugolix group discontinued from the study due to a nonserious grade 2 adverse event of constipation, and no patients withdrew due to an adverse event of diarrhea.

The median duration of adverse events of constipation was relatively shorter in the relugolix group compared with that in the leuprolide group (66.5 and 92.5 days,

respectively). The median duration of diarrhea was longer in the relugolix group compared with the leuprolide group (9.0 and 3.0 days, respectively).

Most adverse events of arthralgia were mild or moderate (grade 1 or grade 2) in severity with grade 3 adverse events of arthralgia reported for two patients (both in the relugolix group); none of the adverse events of arthralgia were serious or led to study drug interruption or withdrawal.

An analysis was done to evaluate adverse events before and after the concomitant use of enzalutamide (16 patients), docetaxel (7 patients), or radiotherapy (99 patients) because both medications and radiotherapy are frequently used in combination with ADT for the treatment of advanced prostate cancer. No clinically relevant differences were noted in the incidence or types of adverse events within treatment groups before or after concomitant use of enzalutamide, docetaxel, or radiotherapy in either treatment group.

Hypertension was the most commonly reported grade ≥ 3 adverse event and was reported in a higher proportion of patients in the relugolix group (1.6%) than in the leuprolide group (0.6%). However, the overall incidence of adverse events of hypertension was lower in the relugolix group (7.9%) compared with the leuprolide group (11.7%). The proportion of patients who had an increase in systolic blood pressure ≥ 20 mmHg and diastolic blood pressure ≥ 15 mmHg from baseline was 15.1% and 8.4%, respectively in the relugolix group compared to 15.9% and 10.7%, respectively in the leuprolide group. All other grade ≥ 3 adverse events were reported with similar incidence in both treatment groups.

The overall summary of adverse events for the Prostate Cancer 48-Week Safety Population was generally consistent with that for study MVT-601-3201 with no new safety findings.

In study C27003 a lower proportion of patients in the relugolix group than in the degarelix group was reported to have had at least one adverse event (86% vs. 97%), a grade 3 or higher adverse event (2% vs. 11%), a grade 3 or higher adverse event related to study drug (0% vs. 3%), or any serious adverse event (2% vs. 8%). The most common ($\geq 10\%$ of patients) adverse events in the relugolix group were hot flush (relugolix 57%, degarelix 61%), fatigue (relugolix 26%, degarelix 16%), diarrhea (relugolix 18%, degarelix 13%), cataract (relugolix 15%, degarelix 18%), nocturia (relugolix 14%, degarelix 13%), and pollakiuria (relugolix 12%, degarelix 16%).

The Applicant's Position:

Relugolix was generally well-tolerated, with a safety profile consistent with the known effects of low testosterone concentrations.

The overall incidence of adverse events was comparable between the relugolix group and the leuprolide group. Most adverse events were also expected adverse events with the use of ADT, including hot flush, fatigue/asthenia, weight increased, insomnia, and

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hyperhidrosis (Lupron Prescribing Information 2019; Firmagon Prescribing Information 2020). The most frequently reported adverse event for patients who received relugolix and leuprolide was hot flush.

All adverse events reported for $\geq 5\%$ of patients in either treatment group were reported in similar proportions of patients in both groups, with the exception of constipation, diarrhea, and arthralgia reported relatively more frequently, and hypertension reported relatively less frequently.

No clinically relevant differences were noted in the incidence or types of adverse events within treatment groups before or after concomitant use of enzalutamide, docetaxel, or radiotherapy in either treatment group.

The FDA's Assessment:

Adverse reactions occurring in at least 10% of patients on the relugolix arm of HERO, including grouped preferred terms, are presented in Table 24. The incidences of adverse events were similar between the relugolix and leuprolide arms and were generally consistent with class effects of androgen deprivation therapy. The FDA agrees that while the preferred term of hypertension was reported in more patients on the relugolix arm, there was no meaningful difference when considering changes in either measured systolic or diastolic blood pressure. Additionally, there was no increase in cardiac events in the relugolix arm, as previously discussed.

Table 24: Adverse reactions in >10% of patients treated with relugolix in HERO

Adverse Reaction	Regolix N = 622		Leuprolide Acetate N = 308	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Vascular disorders				
Hot flush	54	0.6	52	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ^a	30	1.1	29	1.6
General				
Fatigue ^b	26	0.3	24	0
Gastrointestinal disorders				
Diarrhea ^c	12	0.2	7	0
Constipation	12	0	10	0

^a Includes arthralgia, back pain, pain in extremity, musculoskeletal pain, myalgia, bone pain, neck pain, arthritis, musculoskeletal stiffness, non-cardiac chest pain, musculoskeletal chest pain, spinal pain, and musculoskeletal discomfort.

^b Includes fatigue and asthenia

^c Includes diarrhea and colitis

Laboratory Findings

Data:

Hematology

In study MVT-601-3201, mean hematology laboratory values at baseline and subsequent time points were generally consistent across the treatment groups for all parameters. Furthermore, for hematology laboratory parameter shifts from baseline, observed values were generally consistent across treatment groups with most values being in the normal range (ie, grade 0) for most parameters.

Hemoglobin

Median hemoglobin levels at baseline were within the normal range for both groups: 144.0 g/L in relugolix group and 143.0 g/L in leuprolide group. The median hemoglobin levels at Week 49 Day 1 (Day 337) decreased by approximately 10 g/L compared with baseline levels in both groups (median of 134.0 g/L in relugolix group and 133.5 g/L in leuprolide group). Most patients in relugolix and leuprolide groups had a decrease of > 1 g/dL from baseline in hemoglobin during the study (68.8% and 67.5%, respectively).

The proportion of patients with hemoglobin \leq 10.5 g/dL after baseline were similar in relugolix (4.8%) and leuprolide groups (5.5%). A small proportion of patients (0.5% in the relugolix group and 0.6% in the leuprolide group) had grade 0, 1, or 2 anemia at baseline and developed grade \geq 3 anemia during the study.

Platelets

Median platelet values at baseline were similar in the relugolix group ($218.5 \times 10^9/L$) and the leuprolide group ($214.0 \times 10^9/L$) and slightly increased at Week 49 Day 1 (Day 337) in both groups ($226.0 \times 10^9/L$ and $222.0 \times 10^9/L$, respectively). A smaller proportion of patients who received relugolix (2.7%) developed platelet levels less than the lower limit of normal during the study compared with patients who received leuprolide (5.8%). Patients who had platelet values $< 100 \times 10^9/L$ during the study were comparable in both groups (0.5% in relugolix group and 0.6% in leuprolide group).

Except for the previously mentioned differences in hematology parameters, the remaining parameters were comparable between the treatment groups. The pattern of the proportion of patients with hematology laboratory parameters meeting predefined limits of change based on last observation on treatment was similar to the pattern observed for hematology parameters meeting predefined limits of change at any time.

In study C27003, mean hemoglobin levels declined over time for both the relugolix group and degarelix group. At baseline, mean hemoglobin was 14.5 g/dL in the relugolix group and 14.3 g/dL in the degarelix group. At Week 25 Day 1 (Day 169), mean hemoglobin in each group was 13.1 g/dL in the relugolix group and 12.9 g/dL in the degarelix group. Neutrophil counts decreased in both groups over time; 3% of patients in each group were reported to have a shift from grade 0 to grade 2 without associated

Relugolix

discontinuation of study drug treatment. The maximum postbaseline shift in platelet count was grade 1 (relugolix 14%, degarelix 21%).

In the pooled analysis population (MVT-601-3201 and C27002) as well as in individual supportive studies, there were no clear imbalances or trends in changes of hematology parameters following treatment with relugolix.

Chemistry

In study MVT-601-3201, mean chemistry laboratory values at baseline and subsequent time points were generally consistent across the treatment groups for all parameters. Furthermore, for chemistry laboratory parameter shifts from baseline, observed values were generally consistent across treatment groups with most values being in the normal range (ie, grade 0) for most parameters.

Findings in the 48-Week safety pool were consistent with the pivotal study. In general in Study C27003, most shifts observed in serum chemistry values did not exceed one CTCAE grade from baseline to postbaseline values with the exception of glucose, which showed a shift from baseline grade 0 to postbaseline grade 3 in one patient in the relugolix group. Additionally, two patients (3%) in the relugolix group and one (3%) in the degarelix group had a shift in glucose from grade 0 to 2.

AST, ALT, and Bilirubin

Mean changes in ALT and AST over time in the relugolix and leuprolide groups were similar. The proportions of patients with laboratory values meeting predefined limits of change at any time ALT or AST were also similar in both treatment groups.

Patients with any postbaseline ALT or AST elevations were similar between the treatment groups. There were no patients with bilirubin increase of $> 2 \times$ ULN in either relugolix or leuprolide groups. No patient had either ALT and/or AST $\geq 3 \times$ ULN and total bilirubin $> 2 \times$ ULN with or without alkaline phosphatase $< 2 \times$ ULN (ie, there were no events meeting the definition of Hy's law). Most patients in both groups with ALT or AST elevations had confounding factors or alternate etiologies.

Alanine aminotransferase increased (relugolix 4.2%, leuprolide 2.6%) is listed in the proposed prescribing information as an adverse drug reaction associated with relugolix.

Glucose and HbA1c

In general, mean glucose concentrations increased progressively from baseline over the 48-week treatment period in both groups, with an overall mean increase at the Week 49 Day 1 (Day 337) visit of 0.39 mmol/L in the relugolix group and an overall mean increase of 0.51 mmol/L in the leuprolide group. The relugolix treatment group had consistently lower relative incidences of glucose excursions from baseline compared to the leuprolide treatment group to ≥ 150 mg/dL (16.7% and 22.1%, respectively), ≥ 200 mg/dL (7.4% and 13.0%, respectively), and ≥ 250 mg/dL (3.1% and 6.8%, respectively).

The mean and median HbA1c at baseline were in the prediabetic range (5.8% and 5.7% in the relugolix group; 5.9% and 5.7% in the leuprolide group) in both groups and increased in a similar proportion in the relugolix (0.31% and 0.20%) and leuprolide (0.26% and 0.20%) groups, respectively, over the 48-week treatment period. The proportion of patients with an HbA1c increase of greater than 1% from baseline at any time was comparable in the relugolix (7.2%) and leuprolide (6.8%) groups.

In study C27003, mean HbA1c was 5.9% in the relugolix group and 6.0% in the degarelix group with median 5.8% in each group, thus in the prediabetic range. Median increases in HbA1c from 0.1% to 0.3% were observed in each group with the greatest relative increase observed at Week 13.

Lipids

Median total cholesterol, low-density lipoprotein cholesterol, triglyceride and high-density lipoprotein cholesterol levels at baseline were similar in both groups and remained at similar levels at Week 49 Day 1 (Day 337). A similar proportion of patients in both groups had a total cholesterol greater than baseline values and > 200 mg/dL during the study (48.9% in the relugolix group and 44.2% in the leuprolide group).

A similar proportion of patients in relugolix and leuprolide groups who had normal baseline low-density lipoprotein cholesterol had postbaseline levels that were ≥ 4.921 mmol/L during treatment (2.7% and 1.6%, respectively). A similar proportion of patients in both groups had postbaseline triglyceride levels greater than baseline and > 200 mg/dL during the study (29.5% in the relugolix group and 29.2% in the leuprolide group).

No clinically meaningful differences in measures of lipid metabolism were observed between groups over 48 weeks of treatment.

Creatinine

Median creatinine levels at baseline were similar in the relugolix and leuprolide groups (83.0 μ mol/L and 84.0 μ mol/L, respectively) and remained similar at the Week 49 Day 1 (Day 337) (81.0 μ mol/L and 80.0 μ mol/L). A small and similar proportion of patients in both groups demonstrated a creatinine postbaseline value > 1.5 mg/dL and above baseline values (4.5% in relugolix group and 4.9% in leuprolide group). Both groups had an even smaller proportion of patients with a greater than 50% increase in creatinine from baseline (1.6% and 1.0%, respectively).

The Applicant's Position:

All clinical laboratory tests conducted throughout the clinical development program and specifically the pivotal phase 3 study, including hematology, chemistry, urinalysis, and lipids, were comparable between the two groups. In the analyses for carbohydrate (glucose) metabolism, while there were no differences in change from baseline for HbA1c (> 1% increase from baseline in relugolix group [7.2%] and leuprolide group [6.8%]), a smaller increase from baseline in mean glucose was observed, as well as

Relugolix

fewer patients meeting predefined limits of change for glucose in the relugolix group compared with the leuprolide group.

The FDA's Assessment:

Laboratory abnormalities worsening from baseline were similar between the relugolix and leuprolide arms and were consistent with class effects of androgen deprivation therapy, including increased glucose and dyslipidemia (Table 25). The incidence of hepatic transaminase elevation was similar between the two arms.

Table 25: Laboratory abnormalities in >15% of patients treated with relugolix in the HERO study

Laboratory Test	Relugolix ^a		Leuprolide Acetate ^a	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Chemistry				
Glucose increased	44	2.9	54	6
Triglycerides increased	35	2	36	0.7
ALT increased	27	0.3	28	0
AST increased	18	0	19	0.3
Hematology				
Hemoglobin decreased	28	0.5	29	0.7

^a The denominator used to calculate the rate varied from 611 to 619 in the relugolix arm and from 301 to 306 in the leuprolide arm based on the number of patients with a baseline value and at least one post-treatment value.

Vital Signs and Body Weight

Data:

In study MVT-601-3201, mean systolic and diastolic blood pressures as well as mean heart rates were generally consistent and comparable across treatment groups at each timepoint throughout the study.

The proportion of patients with a potentially clinically significant abnormality in blood pressure or heart rate values were evenly distributed across treatment groups. The proportion of patients with potentially clinically significant abnormalities reported for two or more consecutive postbaseline visits were also evenly distributed across treatment groups.

Comparable changes from baseline in body weight were observed in both treatment groups over the 48-week treatment period, with a gain of 2.1 kg and 2.0 kg at Week 49 Day 1 (Day 337) in the relugolix and leuprolide groups, respectively.

In the pooled 48-week safety data, there were also no clinically important differences between treatment groups in any prespecified parameter. In study C27003, no clinically significant changes from baseline were observed in the mean values of vital signs.

The Applicant's Position:

No difference in potentially clinically significant changes from baseline were observed in the mean values of vital signs following treatment with relugolix compared to the comparator during relugolix development program studies for the treatment of advanced prostate cancer. Weight increased is listed in the proposed prescribing information as an adverse drug reaction associated with relugolix.

The FDA's Assessment:

The FDA agrees with the Applicant's position above.

Electrocardiograms

Data:

The ECG data were not pooled and are presented individually for the four clinical studies in patients with prostate cancer.

In study MVT-601-3201, 12-lead ECGs were obtained at the screening visit, the baseline (Day 1), Week 5, Week 13, Week 25, Week 49/early termination visit, and the safety follow-up visit. A comparable proportion of patients between the two groups had an ECG that was interpreted as abnormal and clinically significant (27 patients [4.3%] in the relugolix group and 9 patients [2.9%] in the leuprolide group).

In study C27002, ECGs were obtained throughout the study and interval data were entered into the database. During the study, a change in QTcF was ≥ 30 msec for 9% to 21% of patients in the combined 80-mg and 120-mg relugolix groups, respectively, and leuprorelin results were similar. The incidence of a change from baseline ≥ 60 msec was $\leq 3\%$ for the combined 80-mg and 120-mg relugolix group at any study visit; eight patients (7%; four patients per 80-mg dose level and four patients per 120-mg dose level) in the combined relugolix group had a maximum change from baseline ≥ 60 msec at some time during the study. No patient in the leuprorelin group had a change from baseline of ≥ 60 msec. No patient in the study had an adverse event reported based on ECG results. The ECG data from this study demonstrated a comparable castration-related effect on QTc between treatment groups, with no apparent additional risk identified with the small molecule attributes of relugolix relative to the GnRH receptor agonist, leuprolide.

In study C27003, the majority of patients had QTcF values below 450 msec throughout the study. A change from baseline in QTcF ≥ 30 msec was observed for approximately 10% of patients in the relugolix group for each study visit and between 8% to 24% of patients in the degarelix group for each study visit. One patient (2%) in the relugolix group and no patient in the degarelix group had a change from baseline QTcF ≥ 60 msec.

In study TB-AK160108, there were no 12-lead ECG interpretations of abnormal and clinically significant and no QTcF values meeting the protocol-defined upper limit of 500 msec were noted in Part A. In Part B, a 12-lead ECG interpretation of abnormal and clinically significant was reported for one patient in the 80-mg group and one patient in the 120-mg group. These ECGs were reported as adverse events of electrocardiogram QT prolonged and electrocardiogram ST elevated, respectively. Additionally, two patients in the 80-mg group and five patients in the 120-mg group had a QTcF values reported as either above 500 msec or above 460 msec and > 30 msec increase from baseline at some point during the study.

The Applicant's Position:

No clinically significant changes from the baseline were observed in ECGs obtained as part of general safety assessment following treatment with relugolix during the four clinical studies in patients with prostate cancer in the development for the proposed indication of advanced prostate cancer.

The FDA's Assessment:

The FDA agrees with the Applicant's position above.

QT-interval

Data:

The QT-interval and the heart rate-corrected QT (QTc) interval determined using Fridericia's formula (QTcF) were assessed during the four clinical studies in prostate cancer patients. In the dedicated thorough QT/QTc study TAK-385_106, administration of single 60- or 360-mg doses of relugolix (up to the loading dose and three times the recommended daily dose) did not prolong the QTcF interval in healthy subjects (see Section 8.2.8).

The Applicant's Position:

No signal for adverse events associated with QTc prolongation has been identified during the relugolix development program. Study TAK-385_106 demonstrated that relugolix does not prolong the QTc interval.

The proposed prescribing information will include a warning and precaution regarding the potential for prolongation of the QT/QTc interval, as part of a class effect of ADT.

The FDA's Assessment:

The FDA agrees with the Applicant's position above.

Immunogenicity

The Applicant's Position:

Relugolix is not a therapeutic protein and therefore immunogenicity is not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Further to the safety parameters of interest defined and discussed under Safety Parameters of Clinical Interest in Section 8.2.4, there are no other submission-specific safety issues to discuss.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No clinical outcome assessments were conducted to inform safety and tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Subgroup analyses were performed for the pooled analysis population (MVT-601-3201 and C27002) to evaluate the effects of intrinsic factors on adverse events. The intrinsic factors included age, race, ethnicity, diagnosis (presence/absence of metastatic disease), and renal function category.

For completeness, subgroup analyses were also performed for the pivotal phase 3 study MVT-601-3201 safety population using the intrinsic factors (age, body mass index, renal function, and race); however, the discussion below is focused on the subgroup analyses of the larger, pooled population because larger subgroups provide for more meaningful comparisons.

Age

For the relugolix group, the overall distributions of adverse events for the age subgroups of < 65, ≥ 65 to < 75, ≥ 75 to < 85, and ≥ 85 years of age were similar except that the oldest subgroup (≥ 85 years) had the highest incidences of serious adverse events and of adverse events leading to study drug discontinuation. Additionally, the incidence of adverse cardiovascular events was highest for the oldest subgroup (≥ 85 years), 11.5% compared with other age subgroups (ranging from 2.3% and 4.2%), and the incidence of carbohydrate and lipid metabolic effects and mood disorders were highest in the youngest age subgroup < 65 years (12.7% and 11.9%, respectively) compared with the other age subgroups (ranging from 3.8% to 8.7% and from 0% to 4.8%, respectively).

These observations for the oldest subgroup did not appear to be driven by any particular type of adverse event; the sample size for the age subgroup of ≥ 85 years is small (N = 26 for relugolix and N = 15 for leuprolide), thus making comparisons with larger subgroups difficult to interpret. It is expected that a population of men >85 years of age with prostate cancer would be at a higher risk for serious adverse events including death or adverse events leading to discontinuation relative to younger groups with otherwise similar characteristics. No specific patterns were identified in the clinical

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data that would suggest a differential safety profile of relugolix in this subgroup of patients.

Race

The overall distribution of adverse events for the race subgroups (Asian, Black/African American, White) were generally similar, except that the Black/African American subgroup had the highest incidence of adverse events considered to be related to study drug (35/40 patients [87.5%] for relugolix) compared with the White subgroup (367/477 patients [76.9%] for relugolix) or the Asian subgroup (78/128 patients [60.9%] for relugolix). This observation may be driven by the higher incidences of hot flush, fatigue, and weight increased observed for the Black/African American subgroup than for the White and Asian subgroups. Fewer serious adverse events were reported for the Black/African American subgroup (5.0% for relugolix) than for the White subgroup (12.6%) or the Asian subgroup (11.7%). Interpretation of these findings is limited by the small sample size of the Black/African American subgroup (N = 40 for relugolix), thus making comparison with the larger subgroups difficult. Overall, the differences in the adverse event profile of relugolix in subgroups defined by race do not appear to be clinically meaningful.

Ethnicity

The overall distributions of adverse events for the ethnicity subgroups (Not Hispanic or Latino, and Hispanic or Latino) were similar except that the Not Hispanic or Latino subgroup had a higher incidence of serious adverse events (12.2% for the relugolix) compared with the Hispanic or Latino subgroup (5.4%). Conversely, the Not Hispanic or Latino subgroup had a lower incidence of adverse events leading to study drug discontinuation (3.3% for relugolix) compared with the Hispanic or Latino subgroup (7.1%). These observed differences between the two ethnicity subgroups did not appear to be attributable to any specific adverse event.

Regarding safety parameters of interest, the incidence of carbohydrate and lipid metabolic effects was lower for the Not Hispanic or Latino subgroup (7.7% for relugolix) than for those of Hispanic or Latino ethnicity (17.9% for relugolix). No other notable differences were observed for the incidences of safety parameters of interest. It has been previously described that individuals of Hispanic or Latino ethnicity are at a higher risk for abnormal glucose and lipid metabolism relative to those without that ethnic background (Aguayo-Mazzucato et al. 2019).

Prostate Cancer Characteristics (Nonmetastatic or Metastatic)

Data:

The overall distributions of adverse events for the subgroups defined by prostate cancer characteristics (presence/absence of metastatic disease) were similar between the subgroups except that patients with metastatic disease had higher incidences of grade ≥ 3 adverse events and serious adverse events (23.8% and 17.5%, respectively for

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relugolix) compared with patients with no metastatic disease (14.3% and 8.9%, respectively for relugolix). These observations did not appear to be driven by any specific adverse event.

Regarding commonly reported adverse events, the incidence of arthralgia in the relugolix group was notably higher for the subgroup with metastatic disease (17.5%) compared with the subgroup with no metastatic disease (9.1%).

Regarding parameters of clinical interest, no notable differences between the subgroups were observed.

Patients with metastatic disease are at a higher risk for disease progression relative to the patients without metastatic disease and are, therefore, at a higher risk of complications and frequently require more aggressive treatment with multiple medications. No clear patterns of concern were observed between these two groups regarding specific adverse events and the observed differences between these subgroups in the incidences of serious adverse events and adverse events grade ≥ 3 are likely driven by this more advanced disease than any real differences in the safety profile of relugolix.

The Applicant's Position:

Overall, the differences in the adverse event profile of relugolix in subgroups defined by age, race, ethnicity, or prostate cancer characteristics do not appear to be clinically meaningful, or are consistent with known risk factors (eg, abnormal glucose metabolism in persons of Hispanic or Latino heritage).

The FDA's Assessment:

The FDA agrees with the Applicant's position that there are no clinically meaningful differences demonstrated in the adverse event profile of relugolix in subgroups of age, race, and ethnicity, although the incidence of adverse events was highest in patients over 85 years of age.

Specific Safety Studies/Clinical Trials

Data:

Mild and Moderate Hepatic Impairment Study (MVT-601-1002)

The mild and moderate hepatic impairment study (MVT-601-1002) was an open-label, parallel-cohort, single-dose study to assess the potential effects of mild and moderate hepatic impairment on the pharmacokinetics and safety of relugolix in adult men and women. A total of 24 male and female participants were enrolled and completed the study.

In this study, all reported adverse events were mild in severity and transient in nature. A total of 10 adverse events were reported in 9 of the total 24 participants (37.5%), of which three events (in three participants) were considered by the investigator to be

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drug-related. These drug-related adverse events were all reported in participants with mild hepatic impairment and were related to nervous system disorders and psychiatric disorders including one event of dysgeusia, one event of headache, and one event of euphoric mood (each in one participant). No clinically significant changes in clinical laboratory tests, vital sign measurements or ECG parameters were reported.

There were no deaths, serious adverse events, or discontinuations due to an adverse event in this study.

Moderate Renal Impairment Study (MVT-601-040) and Severe Renal Impairment Study (MVT-601-1003)

The moderate renal impairment study (MVT-601-040) and the severe renal impairment study (MVT-601-1003) were both open-label, parallel-cohort, single-dose studies to assess the potential effects of moderate or severe renal impairment on the pharmacokinetics and safety of relugolix in adult men and women. In the moderate renal impairment study, a total of 24 male and female participants, 18 to 80 years of age, inclusive, were enrolled and completed the study. In the severe renal impairment study, a total of 16 male and female participants, 18 to 75 years of age, inclusive, were enrolled and completed the study.

In the moderate renal impairment study, all reported adverse events were mild in severity and transient in nature. A total of four adverse events were reported in 4 participants of the total 24 participants (16.7%), of which three events (in three participants) were considered by the investigator to be drug-related. These drug-related adverse events were all reported in healthy participants with normal renal function and were related to gastrointestinal disorders and nervous system disorders including two events of somnolence (in two participants) and one event of dry mouth (in one participant). No clinically significant changes in clinical laboratory tests or vital sign measurements were reported.

In the severe renal impairment study, all reported adverse events were mild or moderate in severity and transient in nature. A total of seven adverse events were reported in 5 participants of the total 16 participants (31.3%), of which two events (in two participants) were considered by the investigator to be drug-related. These drug-related adverse events were all reported in healthy participants with normal renal function and were related to general disorders and administration site condition and vascular disorders including one event of edema peripheral (in one participant) and one event of hot flush (in one participant). No clinically significant changes in clinical laboratory tests, vital sign measurements or ECG parameters were reported.

There were no deaths, serious adverse events, or discontinuations due to an adverse event in either study.

Thorough QT/QTc Study (TAK-385_106)

The thorough QT/QTc study (TAK-385_106) was a randomized, double-blind, placebo- and positive-controlled (open-label moxifloxacin), parallel-group study to assess the potential effects of a 60-mg dose and a 360-mg dose of relugolix on QT-interval prolongation in healthy adult men and women. A total of 280 male and female participants were enrolled and 280 participants completed the study.

Administration of single 60- or 360-mg doses of relugolix did not prolong the QTcF interval in healthy adult men and women to a level of regulatory concern. All point estimates for the ddQTcF interval were below 5 msec and the upper bound of the 90% CI were below 10 msec at each postdose timepoint. Adequate assay sensitivity was demonstrated for the moxifloxacin treatment, as the lower bounds of the 90% CI of the mean ddQTcF interval exceeded 5 msec at all postdose timepoints.

The Applicant's Position:

Treatment with relugolix was generally well-tolerated in subjects with mild or moderate hepatic impairment, moderate renal impairment, or severe renal impairment. Relugolix at doses up to 360 mg does not prolong the QTcF interval to a level of regulatory concern.

No safety concerns were noted for these studies.

The FDA's Assessment:

See the clinical pharmacology review (Section 6) for discussion of the pharmacokinetics of relugolix in patients with mild to severe renal and mild to moderate hepatic impairment. The FDA agrees that there are no clinically meaningful differences in the pharmacokinetics in these subgroups. The effect of end-stage renal disease with or without hemodialysis or severe hepatic impairment on the pharmacokinetics of relugolix has not been evaluated.

The FDA agrees that there is no evidence of clinically meaningful QTcF prolongation with relugolix administration. However, QTc prolongation will be added to the Warnings section of labeling given class effects with androgen deprivation therapies.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

The analysis of the occurrence and type of second primary malignancies was performed by review of all terms within the MedDRA system organ class of "Neoplasm Benign, Malignant, and Unspecified (Including Cysts and Polyps)" with manual removal of terms relating to prostate cancer or representing benign conditions. Overall in study MVT-601-3201, second primary malignancies were reported more often in the relugolix group (19 patients [3.1%]) compared with the leuprolide group (three patients [1.0%]), but without a clear imbalance for a specific tumor type. The most common second primary

malignancies in both groups were nonmelanoma skin cancers. In the relugolix group, 12 of 19 patients had nonmelanoma skin cancers (seven patients with basal cell carcinoma and five patients with squamous cell carcinoma of skin/lip carcinoma/Bowen's disease). The remaining seven patients had events of colon cancer, lung cancer, transitional cell urothelial cancer, and melanoma (one patient with two lesions of stage 1 melanoma and melanoma in situ, respectively). Review of the latency for each event showed a fairly even distribution over the 48-week treatment period. None of the events were assessed as related to study drug.

Of the 19 events, two were fatal: one patient with non-small cell lung cancer died on Day 97 and one patient with small cell lung cancer died on Day 347. In the leuprolide group, two of three patients had nonmelanoma skin cancer (one each of basal cell carcinoma and squamous cell carcinoma of skin). The remaining patient had an event of transitional cell carcinoma. None of the events was assessed as related to study drug or fatal and all events had onset after 24 weeks of treatment.

In addition, two events of prostate cancer with neuroendocrine dedifferentiation (coded per MedDRA 22.0 to the preferred term Prostate cancer) were identified in study MVT-601-3201, both in the relugolix group.

No events were identified in study C27002. In study C27003, three relugolix patients (4.6%) reported a second primary malignancy, all within the first 12 weeks of treatment (two patients with squamous cell carcinoma and one patient with basal cell carcinoma) compared with one patient (2.6%) in the degarelix group with malignant mesothelioma reported after 24 weeks of treatment. In study TB-AK10608, one event of esophageal cancer was reported at week 85 in the open-label expansion phase of the study (ie, study Day 597).

The Applicant's Position:

An analysis of second primary malignancies in the pivotal phase 3 study demonstrated a higher incidence in the relugolix group compared with the leuprolide group without a clear imbalance for a specific tumor type. The most common second primary malignancies in both groups were nonmelanoma skin cancers, the most frequently diagnosed cancer, with multiyear latency. Consistent with the very short latency between drug initiation and clinical diagnosis, none of the events in either treatment group were assessed as related to study drug. No association between relugolix or ADT and second primary malignancy has been identified.

The FDA's Assessment:

The FDA agrees that, based on the existing safety database, no association between relugolix and second primary malignancy has been demonstrated. See non-clinical review of carcinogenicity (Section 5.5.3).

Human Reproduction and Pregnancy

The Applicant's Position:

No studies of relugolix have been performed in pregnant women. Based on animal reproduction studies and mechanism of action, the proposed prescribing information advises male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of relugolix.

The FDA's Assessment:

The FDA agrees that the safety and efficacy of relugolix 120 mg have not been established in females and that, based on findings in animals and the mechanism of action, can cause fetal harm and loss of pregnancy when administered to a pregnant female. The FDA agrees with advising male patients with female partners of reproductive potential to use effective contraception during treatment and for two weeks after the last dose of relugolix.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Relugolix has been studied in men with prostate cancer and is proposed for the treatment of men with advanced prostate cancer. Therefore, its safety and efficacy in pediatric patients have not been established. Prostate cancer is rarely or never seen in children.

The FDA's Assessment:

The FDA agrees that relugolix has not been studied in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Overdose

In the phase 3 study MVT-601-3201, an overdose was defined as a known deliberate or accidental administration of study drug, to or by a patient, at a relugolix dose above 240 mg within a 24-hour window (excluding the initial loading dose of 360 mg). Four nonintentional and asymptomatic events of overdose were reported in patients treated with relugolix (all in study MVT-601-3201). These doses ranged from 240 mg taken as a single dose to 360 mg taken daily for 13 consecutive days. No adverse events were associated with any of these overdose events.

Drug Abuse

Evidence of the centrally mediated effects typically associated with abuse potential have not been reported in clinical studies during the clinical development of relugolix. Relugolix is a sensitive substrate for P-gp, an efflux transporter responsible for preventing substances from crossing the blood-brain barrier. Relugolix does not cross

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the blood-brain barrier, as evidenced by nonclinical tissue distribution [TAK-385-00081; TAK-385-00082] and quantitative whole-body radiography studies [TAK-385-12448; TAK-385-12449] after oral administration of [¹⁴C]-relugolix to male and female rats. These studies showed that relugolix-related radioactivity is present at only trace amounts in brain and spinal cord, with brain-to-blood ratios < 1, consistent with limited CNS penetration.

Results of an in vitro study evaluating off-target effects in a series of 134 enzyme and radio ligand binding assays suggest there is a low risk for off-target pharmacological effects with relugolix [TAK-385/00054]. Additionally, after administration of a single 2000 mg/kg oral dose of relugolix to male Sprague-Dawley rats in a CNS safety pharmacology study (TAK-385-00069), there were no indications of safety concerns based on general symptoms and behaviors. Otherwise, no specific nonclinical dependence studies have been conducted for relugolix. Relugolix did not bind to any targets associated with neuronal systems related to abuse potential (eg, dopamine, serotonin, gamma-aminobutyric acid, opioid, cannabinoid, N-methyl-D-aspartate, ion-channel complexes, transporters) (TAK-385-00054).

Withdrawal and Rebound

The potential for relugolix to induce withdrawal or rebound events was assessed by comparing adverse events that occurred following the last dose of study drug through the end of the reporting period in patients participating in the testosterone recovery substudy of MVT-601-3201. A total of 137 patients treated with relugolix and 47 patients treated with leuprolide were included in this analysis. Overall, the incidence of adverse events occurring during this portion of the study was slightly higher in the relugolix group (27.7%) compared with the leuprolide group (21.3%), although the majority of event terms were only reported by one patient in either group. The most common adverse event reported during this period was hot flush and occurred in three patients in the relugolix group (2.2%) and one patient in the leuprolide group (2.1%). A review of individual adverse event terms did not reveal any evidence of withdrawal phenomena.

The Applicant's Position:

Overall, a risk of abuse for GnRH receptor agonists and antagonist has not been identified. Based on the mechanism of action of relugolix there is no known drug abuse potential.

In the clinical pharmacology program for relugolix, single doses of up to 360-mg in healthy men and women and multiple doses up to 160 mg once daily for 28 days or 180 mg once daily for 14 days in healthy men were generally safe and well tolerated.

There is no known specific antidote for relugolix overdose. It is not known if relugolix is removed by hemodialysis. In the event of an overdose, stop relugolix and undertake general supportive measures until any clinical toxicity has diminished or resolved. No evidence of withdrawal after treatment discontinuation was identified.

The FDA's Assessment:

The FDA agrees that the abuse potential for relugolix is low and overdose at the doses described by the Applicant did not appear to present a meaningful risk.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Relugolix 120 mg monotherapy for prostate cancer has not been submitted for approval to any health authority.

Relugolix 40 mg monotherapy for the symptomatic treatment of uterine myomas has been submitted and approved only in Japan. The first marketing authorization for relugolix, under the trade name Relumina, was granted to Takeda Pharmaceutical Company Limited in Japan on 08 Jan 2019 for the improvement of symptoms associated with uterine myoma (hypermenorrhea, lower abdominal pain, lower back pain and anemia). Relumina is available as a 40-mg tablet.

Relumina 40 mg was launched in Japan on 01 March 2019. Patient exposure from marketing experience is 8285 patient-years, based on shipping data. The shipment of Relumina since launch (01 March 2019 to 31 December 2019) was (b) (4) tablets.

As of 07 January 2020, 17 serious postmarketing cases had been reported, including two cases of anaphylactic reaction, one case of drug eruption and malaise, one case of hypertension, 12 cases of uterine bleeding events, and one case of uterine myoma expulsion. Note: The two events reported as "anaphylactic reaction" did not meet the diagnostic criteria for anaphylaxis.

The onset latency for the uterine bleeding events was between three days to approximately 3 months after initiation of relugolix monotherapy; the initiation of relugolix treatment relative to the menstrual cycle was unknown. No new safety concerns were identified. Uterine bleeding events, including genital hemorrhage, metrorrhagia, menorrhagia and menstruation disorder are listed as adverse drug reactions in the package insert for Relumina in Japan.

The Applicant's Position:

Relugolix 120 mg monotherapy for prostate cancer has not been approved. Relugolix 40 mg monotherapy for the symptomatic treatment of uterine myomas is approved and marketed in Japan. Based on the review of cumulative safety data, no changes to the conduct of the relugolix clinical program or the Relumina label are warranted. Such events will continue to be actively monitored.

Relugolix

Global literature searches (Medline®, Embase®) have not identified publications containing new safety information regarding relugolix.

The FDA’s Assessment:

Relugolix 120 mg monotherapy has not been previously approved and there is thus no post-marketing experience.

Expectations on Safety in the Postmarket Setting

Data:

The safety of relugolix 120 mg monotherapy was adequately and appropriately assessed in the clinical development for the treatment of the intended broader population with advanced prostate cancer. The safety assessment is primarily based on the pivotal phase 3 study MVT-601-3201 in men with advanced prostate cancer in which relugolix 120 mg was administered orally once daily through 48 weeks of treatment following a single, oral 360-mg loading dose. A total of 624 patients were randomized to receive relugolix and 310 patients to leuprolide, the standard of care ADT.

Three additional clinical studies were conducted in men with prostate cancer and provide evidence in support of the dosing, efficacy and safety analysis of relugolix in the treatment of men with advanced prostate cancer. The clinical pharmacology program consisted of 13 studies in healthy participants, the effect of intrinsic and extrinsic factors on the pharmacokinetics of relugolix, including the effects of renal and hepatic impairment and drug interactions, and the potential effect of relugolix on cardiac repolarization. A pool of six clinical studies with relugolix monotherapy (b) (4) were included for purposes of providing a broader evaluation of hepatic safety.

The Applicant’s Position:

In clinical studies, relugolix was generally well-tolerated, with a safety profile consistent with the known effects of low testosterone concentrations. The most common adverse drug reactions are associated with the mechanism of action, such as hot flush, fatigue, and arthralgia. No new safety concerns were identified with relugolix that are not already known for ADT or observed in the postmarketing setting, and no other is expected in the post marketing setting.

Myovant has comprehensive processes for signal detection, including regular safety reviews, identifying and evaluating issues potentially affecting patient safety, and developing safety recommendations (including changes to the reference safety information). In addition, these processes enable the identification of safety topics that require surveillance. Safety signal detection activities include review of reported adverse events from postmarketing sources, and review of the published literature relevant to relugolix, which are monitored for identification of new safety concerns.

Relugolix

Data from study MVT-601-3201 demonstrate that relugolix has the potential to provide a clinically meaningful improved benefit/risk profile compared with leuprolide, the standard of care for ADT. The risk for major adverse cardiovascular events was 54% lower with relugolix compared with the GnRH receptor agonist leuprolide, while demonstrating superior efficacy with a higher proportion of men achieving and maintaining castrate levels of testosterone from Day 29 through 48 weeks of treatment. Relugolix was not associated with the testosterone surge and potential clinical flare observed with GnRH receptor agonists. Relugolix is administered as an oral formulation, which does not result in injection site reactions like those seen with use of degarelix.

The FDA's Assessment:

The FDA agrees that there are no concerns that safety in the post-marketing setting will meaningfully differ from that observed in clinical trials.

8.2.10. Integrated Assessment of Safety

Data:

Evaluation of the safety of relugolix is primarily based on the pivotal phase 3 study MVT-601-3201 in men with advanced prostate cancer. This pivotal phase 3 study provides a strong basis for evaluation of safety due to the large sample size of patients exposed to relugolix (622 patients were treated with relugolix of whom 563 patients completed the 48 week treatment) in the proposed indication and the randomized controlled study design that allows for a comparison of relugolix with leuprolide, the current standard of care. The safety data from the Week-48 Safety Pool (MVT-601-3201 and C27002 in advanced prostate cancer), C27003 in intermediate-risk, localized disease requiring 6 months of neoadjuvant/adjuvant ADT to EBRT and the dose-ranging study (TB-AK160108) in prostate cancer in general demonstrated a consistent safety profile.

Relugolix was generally well-tolerated, with a safety profile consistent with the known effects of low testosterone concentrations. The overall incidence of adverse events was comparable between treatment groups with at least one adverse event reported for 578 patients (92.9%) in the relugolix group and 288 patients (93.5%) in the leuprolide group. No meaningful differences in the adverse event profile of relugolix were observed between groups in patients who received concomitant enzalutamide, docetaxel, or radiation therapy in this study.

Adverse events grade ≥ 3 , adverse events grade ≥ 3 related to study drug, serious adverse events, and serious adverse events related to study drug were reported with similar frequencies across the treatment groups.

Hypertension was the most commonly reported grade ≥ 3 adverse event and was reported in a higher proportion of patients in the relugolix group (1.6%) than the leuprolide group (0.6%). However, the summary of patients with clinically significant abnormalities in systolic and diastolic blood pressure did not demonstrate any difference in hypertension between the two groups.

All other grade ≥ 3 adverse events were reported with similar incidence in both treatment groups. There were fewer fatal events in the relugolix group (1.1%) than in the leuprolide group (2.9%). The incidence of serious adverse events was similar between the two groups (12.2% vs. 15.3%, respectively). The rate of adverse events that led to withdrawal of study treatment or fatal outcome was comparable between the relugolix group (3.7%) and the leuprolide group (3.2%).

A prespecified safety analysis determined the incidence of unadjudicated MACE on study using a MACE composite query including non-fatal myocardial infarction, non-fatal stroke, and death from any cause. After 48 weeks of treatment, the MACE rate was 2.9% in the relugolix group and 6.2% in the leuprolide group, with 54% risk reduction (HR = 0.46, 95% CI: 0.24, 0.88) in the relugolix group. Of patients reporting a medical history of MACE, the odds of developing MACE during treatment in the leuprolide group was approximately 5.8 times higher than that in the relugolix group. Except for vasomotor symptoms, which was reported for 56.1% of patients in the relugolix group and 54.9% of patients in the leuprolide group, no safety parameter of interest was reported for $\geq 10\%$ of patients in either group. See Section 8.2.4.5.

Events associated with mood disorders, bone mineral density loss, QTc prolongation, and those potentially associated with hypersensitivity were reported in similar proportions of patients for both groups, as per SMQs. Overall, the data suggest that relugolix is associated with lesser impact on glucose metabolism compared with leuprolide and similar effects to those of leuprolide regarding lipid metabolism.

Hepatic transaminase elevations were reported as adverse events for a higher proportion of patients in the relugolix group compared with the leuprolide group (7.6% vs. 5.5%, respectively). However, mean changes from baseline in mean ALT and AST concentrations and the incidence of adverse events of clinical interest (ALT or AST $\geq 3 \times$ ULN) were similar in both groups with no events associated with elevated bilirubin. No evidence of drug-induced liver injury was observed.

All clinical laboratory tests conducted throughout the study except for changes in glucose metabolism were comparable between the two groups (see Section 8.2.4).

There were also no notable findings in physical examinations including assessments of visual acuity.

The Applicant's Position:

The overall evaluation of risks associated with relugolix 120 mg is primarily based on data from the pivotal phase 3 study in patients with advanced prostate cancer, summarized previously, data from the supportive phase 1 and phase 2 studies in patients with prostate cancer, data from the clinical pharmacology studies in healthy participants and patients with renal or hepatic impairment, and data from the nonclinical program.

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In general, the safety profile of relugolix 120 mg in men with advanced prostate cancer is characterized by signs and symptoms associated with the hypoandrogenic state resulting from treatment with a GnRH receptor antagonist.

Persistently low testosterone concentrations like those achieved with ADT (< 50 ng/dL) are associated with well-established signs and symptoms including sexual dysfunction, vasomotor symptoms, bone mineral density loss, fatigue, abnormalities of glucose and lipid parameters, gynecomastia, potential increase in cardiovascular risk, anxiety, and mood disorders.

The most common adverse drug reactions are associated with the mechanism of action, such as hot flush, fatigue, and arthralgia. Additionally, nonspecific gastrointestinal symptoms including constipation, diarrhea, and nausea, were reported with relugolix treatment in more than 5% of patients. These findings are more likely associated with the patient population and the condition being treated. These adverse events were generally mild to moderate in severity, short in duration, and did not lead to discontinuation of study drug.

Hypertension was reported for > 5% of patients in the relugolix group but at a lower frequency than that observed in the leuprolide group. No meaningful differences were observed between groups in mean changes from baseline in blood pressure or in the proportion of patients with blood pressure values considered to be abnormal and clinically significant.

Hepatic transaminase elevations (asymptomatic, predominantly grade \leq 2 and transient) have been reported for < 1% of participants in relugolix program studies; such transient serum transaminase elevations have been noted with other GnRH analogues.

Relugolix is the first GnRH receptor antagonist to demonstrate a reduced risk of MACE compared to leuprolide in a large, prospective, randomized phase 3 clinical trial, MVT-601-3201. Relugolix treatment was associated with a substantial reduction in unadjudicated MACE as compared with leuprolide treatment (2.9% vs. 6.2%, respectively) over the 48 weeks of study treatment. The long-term impact of relugolix on cardiovascular morbidity and mortality is not known.

Relugolix offers the additional safety advantages of rapid onset of action without a testosterone surge avoiding the risks associated with clinical flare, the coadministration of an antiandrogen, with the added convenience oral dosing while avoiding injections and the risk of injection site reactions. Furthermore, this oral treatment does not require regular in-person visits to the clinic for injections, a potential advantage to men with advanced prostate cancer. The clinical pharmacokinetic and pharmacodynamic profiles of relugolix, with rapid onset of testosterone suppression and an effective half-life of 25 hours, permit relatively rapid return of testosterone to normal levels following discontinuation, an additional safety advantage compared with available depot peptide ADT formulations.

Overall, relugolix was generally well-tolerated; the most common adverse events occurring in patients with prostate cancer receiving 48 weeks of relugolix included vasomotor symptoms, fatigue, diarrhea, constipation, and arthralgia. Importantly, relugolix demonstrated a lower risk of prospectively defined major adverse cardiovascular events, compared with leuprolide-treated patients.

The FDA's Assessment:

The FDA review of the safety of relugolix was primarily based on the results of the HERO study. The review team agrees with the Applicant's description of the common and severe adverse events in HERO. Overall, the safety profile of relugolix in the HERO study was similar to that of leuprolide with no new safety signals observed beyond those expected based on the class of GnRH analogs, i.e. adverse events consistent with androgen deprivation, such as hot flush and metabolic derangements. As noted previously, the FDA does not agree with the Applicant's claim regarding improved cardiac safety of relugolix as compared to leuprolide as the study was not designed to assess this claim. While the incidence of major adverse cardiovascular events, including fatal and non-fatal myocardial infarction and stroke, appeared lower on the relugolix arm, the FDA considers these findings exploratory. The HERO study was not designed to evaluate the safety of treatment with relugolix beyond 48 weeks; however, the review team does not expect the safety profile to differ markedly with extended therapy from that observed with GnRH analogs, which includes adverse reactions secondary to androgen deprivation. Organ impairment studies in patients with moderate to severe renal and mild to moderate hepatic impairment did not demonstrate clinically meaningful pharmacokinetic or safety issues. While no QT/QTc effects were noted, a warning common to all GnRH analogs regarding QT/QTc prolongation will be included in labeling.

Overall, the review team considered the safety profile of relugolix to be acceptable for the treatment of patients with advanced prostate cancer.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

FDA efficacy evaluation was based on data from the HERO study. Study HERO met its primary objective of achieving and maintaining castration (testosterone suppression to < 50 ng/dL) while on study treatment (from Week 5 Day 1 through 48 weeks) by demonstrating that the lower bound of the 95% CI around the cumulative probability of castration rate at the end of 48 weeks was greater than 90%. The results were supported by sensitivity analyses and subgroup analyses. FDA does not accept the first key secondary endpoint of sustained castration rate (non-inferiority test between relugolix and leuprolide), (b) (4)

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(b) (4) Another issue for conducting the non-inferiority comparison is that different censoring rules were used in historical trials and study HERO. As the proposed non-inferiority comparison was not acceptable, no further claims could be made on this comparison including a superiority claim that was not pre-specified in the study statistical analysis plan. Results of other secondary endpoints were supportive.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The efficacy and safety results are adequate to support the use of relugolix as an androgen deprivation treatment for patients with advanced prostate cancer. The review team recommends regular approval for relugolix at an initial dose of 360 mg once followed by 120 mg daily for the treatment of patients with advanced prostate cancer.

X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

Primary Clinical Reviewer

Clinical Team Leader

9 **Advisory Committee Meeting and Other External Consultations**

The FDA's Assessment:

This application was not presented to the Oncologic Drug Advisory Committee.

10 Pediatrics

The Applicant's Position:

Relugolix was not studied in pediatric patients. The FDA accepted the agreed initial pediatric study plan (14 Jan 2019), and a request for a full waiver of pediatric studies in males and females < 17 years of age is included in this application in Module 1.9.1.

The FDA's Assessment:






The FDA agrees with the Applicant's position.

11 Labeling Recommendations

The FDA's Assessment:

The following table summarizes key changes in labeling made during review of relugolix. Only significant (high level) changes are included and not direct quotations. Please see full label for further information.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Highlights of Prescribing Information	<ul style="list-style-type: none"> Most common adverse reactions listed only included hot flush, fatigue, constipation, diarrhea, and arthralgia 	<ul style="list-style-type: none"> Most common adverse reactions updated based on pooled preferred terms and laboratory abnormalities
Section 1, Indications and Usage	<ul style="list-style-type: none"> (b) (4) 	<ul style="list-style-type: none"> (b) (4) indication shortened to treatment of adults with advanced prostate cancer
Section 2, Dosage and Administration	...	<ul style="list-style-type: none"> Split into Section 2.1, Recommended Dosage and Section 2.2, Dose Modifications
Section 5, Warnings and Precautions	<p>Stated animal reproductive studies and mechanism of action can cause fetal harm and loss of pregnancy</p> <p>Information on contraception use duration was provided</p>	<ul style="list-style-type: none"> Revised text under Embryo-Fetal Toxicity (5.2) to include information on rabbits and provide animal to human exposure multiples at the recommended human dose

		<ul style="list-style-type: none"> •  (b) (4) • Added Section 5.3, Laboratory Testing to include information on diagnostic gonadotropic and gonadal function testing and PSA testing
<p>Section 6, Clinical Trials Experience</p>	<ul style="list-style-type: none"> • The exposure rate to relugolix in the 48-week study was modified in which 91% of the patients completed the study • Fatal and non-fatal myocardial infarction and stroke were reported in  (b) (4) % of patients receiving TRADENAME 	<ul style="list-style-type: none"> • Modification accepted to reflect updated exposure rate of 91% in the 48-week study • The percentage of fatal and non-fatal myocardial infarction and stroke were updated to 2.7%
<p>Section 7, Drug Interactions</p>	<ul style="list-style-type: none"> •  (b) (4) •  	<ul style="list-style-type: none"> •  (b) (4) •

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	(b) (4)	(b) (4)
Use in Specific Populations	<p>Provided information on (b) (4) rabbit (b) (4) exposures for both species</p> <p>Provided Animal Data in 8.2</p>	<ul style="list-style-type: none"> Revised the Risk Summary in 8.1 to discuss embryo-fetal toxicities from relevant animal studies only and provide animal to human exposure multiples at recommended human dose Revised Animal Data in 8.1 to more clearly outline fetal effect in rabbits and provided animal to human exposure multiples at recommended human dose (b) (4) <p>(b) (4)</p> <ul style="list-style-type: none"> Revised Animal Data in 8.2 to provide a more concise summary Added references to the Clinical Pharmacology in 8.3
Section 8.5 Geriatric Use	<ul style="list-style-type: none"> Information included based on 	<ul style="list-style-type: none"> Updated to evaluate

	patients (b) (4) 75 years of age	information based on patients using age cut-off of 65 years and older
<div style="text-align: right;">(b) (4)</div>		
Section 12.1 Mechanism of Action	<div style="text-align: right;">(b) (4)</div>	
Section 12.3 Pharmacokinetics	<div style="text-align: right;">(b) (4)</div>	
Nonclinical Toxicology	Included information that no effects on fertility or reproductive organs in males in rat studies	<ul style="list-style-type: none"> • Corrected the exposure multiples in carcinogenicity studies • (b) (4) • Included animal to human exposure

		<p> multiples at recommended human dose for monkey study</p> <ul style="list-style-type: none"> Included phospholipidosis findings in animal studies and animal to human exposure in 13.2
<p>Section 14, Clinical Studies</p>	<p>...</p>	<ul style="list-style-type: none"> Language describing primary endpoint was clarified. Language describing secondary endpoints clarified. Table 4 (new Table 3) (b) (4) (b) (4) Figure 4 (new Figure 2) changed to depict mean percent change from baseline in T concentrations Table 5 (new Table 4) (b) (4) (b) (4) New Figure 3 added to depict Cumulative incidence of time

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		<p>to testosterone <50 ng/dl and <20 ng/dl, respectively</p> <ul style="list-style-type: none"> • Table 6 depicting (b) (4) • Information regarding testosterone recovery edited (b) (4) • •
<p>Section 17, Patient Counseling Information</p>	<p>...</p>	<ul style="list-style-type: none"> • Updated to reflect changes made to label in sections noted above

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

No REMS is recommended for this application.

13 Post Marketing Requirements and Commitment

The FDA's Assessment:

The product quality review team requested, and the Applicant agreed to, the following post-marketing commitment:

1. PMC 3962-1: Submit test report for the currently ongoing study titled "The Zebrafish Extended One-Generation Reproduction Test" to support of the environmental risk assessment for relugolix

The Applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb.

(b) (4)
(b) (4)

The clinical pharmacology team requested, and the Applicant agreed to, the following post-marketing commitment:

2. Conduct a pharmacokinetic study to evaluate the effect of P-gp inhibitors when administered after relugolix to further inform dosing strategy. Submit the datasets with the final study report. The study results may inform product labeling.

The review team considers the Applicant's proposed labeling regarding dose modification and separation when co-administered with P-gp inhibitors acceptable;

(b) (4)

The milestones for this PMC are as follows:

Draft Protocol Submission: 03/2021
Final Protocol Submission: 06/2021
Study Completion: 01/2022
Final Report Submission: 04/2022

14 Division Director (DHOT) (NME Only)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

I concur with the recommendations of the review team that this application be approved with the agreed-upon labeling.

X

18 Office Director (or designated signatory authority)

X

19 Appendices

19.1. References

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The FDA's References

Cocks K et al. *J Clin Oncol*. 2011 Jan 1; 29(1): 89-96.

19.2. Financial Disclosure

The Applicant's Position:

A Certification/Disclosure of Financial Interests/Arrangements of Clinical Investigators was completed by each investigator for each study.

The FDA's Assessment:

The Applicant provided financial disclosure information for HERO. There were a total of 976 investigators identified, of which 1 was noted to have disclosable financial interests or arrangements. There were two investigators who did not return Form 3455 but neither of them were paid for their involvement in the study and had limited to no involvement, per the Applicant. Given that only one investigator had disclosable interests, it is unlikely that the reported financial disclosure led to significant bias in the conduct of the study or influenced the outcome assessment.

Clinical Study: MVT-601-3201

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 976		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>		
Significant payments of other sorts: <u>1</u>		
Proprietary interest in the product tested held by investigator: <u>0</u>		
Significant equity interest held by investigator in study: <u>0</u>		
Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>2</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Note: Two sub-investigators did not return Form FDA 3455. Neither were paid for their services and each had either minimal or no study engagement.

NDA/BLA Multi-disciplinary Review and Evaluation: NDA 214, 621
Relugolix

Clinical Study: C27003

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>192</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in study: <u>0</u></p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request explanation from Applicant)

NDA/BLA Multi-disciplinary Review and Evaluation: NDA 214, 621
Relugolix

Clinical Study: C27002

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 164		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in study: <u>0</u></p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request explanation from Applicant)

Clinical Study: TB-AK160108

Was a list of clinical investigators provided:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>N/A</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>N/A</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>N/A</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in study: <u>N/A</u> Sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

The FDA's Assessment:

[FDA will complete this section.]

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

Pharmacometrics Review

PopPK Summary

In general, the applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 1.

Table 26. Specific Comments on Applicant’s Final Population PK model

Utility of the final model			Reviewer’s Comments
Support applicant’s proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	“Results from simulations using a population pharmacokinetic (PopPK) model demonstrated no effect of age or body weight on relugolix exposure ($AUC_{0-\tau}$ and C_{trough}). Simulated exposures in Asian and White race were similar, whereas the Black/African American race was associated with a 26% and 16% higher $AUC_{0-\tau}$ and C_{trough} , respectively, compared with the White race. The increase in exposure to relugolix is not considered clinically meaningful.”	The statements are acceptable without significant changes.
	Extrinsic factor	NA	The conclusions on extrinsic factors were not based on PopPK analyses.
Derive exposure metrics for Exposure-response analyses	N.A.		Observed relugolix concentrations were used in PK/PD analysis.
Predict exposures at alternative dosing regimen	NA		NA

Objectives: Use the population pharmacokinetic and pharmacokinetic-pharmacodynamic models for relugolix for the treatment of prostate cancer to support the dose regimen justification of relugolix and aim to:

- Describe the population pharmacokinetics of relugolix in healthy men and prostate cancer patients.
- Identify demographic or physiological covariates that impact pharmacokinetic parameters and explain interindividual variability in relugolix exposure.
- Characterize the relationship between relugolix exposure and testosterone concentrations
- Identify demographic or physiological covariates that impact pharmacodynamic parameters and **APPEARS THIS WAY ON ORIGINAL** explain interindividual variability in testosterone concentrations.
- Describe the time course of testosterone suppression and recovery following initiation and **APPEARS THIS WAY ON ORIGINAL** discontinuation of relugolix treatment.
- Conduct simulations using the final PopPK/PD model to assess the impact on testosterone suppression of treatment-related factors, including relugolix dosing regimen, relugolix clearance modulation (potentially reflecting drug-drug interactions), missed doses and treatment discontinuation, and of any identified covariates.

Data: The PopPK analysis included data from a total of five clinical studies with relugolix: two phase 1 studies (TBAK160108 and C27001 (Part 3 and Part 4)), two phase 2 studies (C27002 and C27003), and one phase 3 study (MVT-601-3201), comprising a total of 912 participants being administered relugolix at dose levels of 60, 80, 120 or 160 mg QD, in most subjects preceded by a single loading dose of 320 or 360 mg on Day 1. The population PK/PD analysis included 899 participants with both PK and testosterone information from the same five clinical studies. The key baseline characteristics of the population are summarized in Table 2.

Table 27. Summary of Baseline Characteristics.

	TB-AK160108 (n=43)	C27001 (n=74)	C27002 (n=110)	C27003 (n=65)	MVT-601-3201 (n=620)	Overall (n=912)
Age (Year)						
Mean (CV%)	74.0 (6.76%)	55.6 (13.9%)	72.2 (12.0%)	70.2 (8.05%)	71.2 (10.9%)	70.1 (12.5%)
Median [Min, Max]	74.0 [65.0, 82.0]	53.5 [45.0, 74.0]	73.0 [49.0, 91.0]	71.0 [52.0, 86.0]	72.0 [48.0, 91.0]	71.0 [45.0, 91.0]
Weight (Kg)						
Mean (CV%)	61.6 (11.4%)	80.5 (11.5%)	91.3 (21.6%)	93.2 (19.2%)	81.5 (20.2%)	82.5 (21.0%)
Median [Min, Max]	61.0 [51.2, 87.7]	79.0 [64.8, 107]	88.7 [56.4, 193]	90.9 [58.2, 146]	80.0 [40.5, 146]	80.6 [40.5, 193]
RACE						
Asian	43 (100%)	2 (2.7%)	3 (2.7%)	0 (0%)	127 (20.5%)	175 (19.2%)

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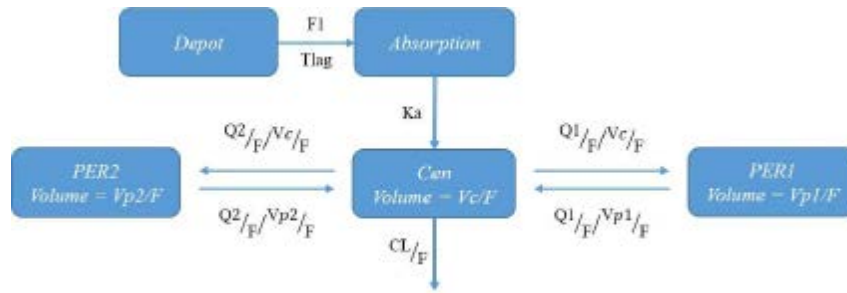
Relugolix

Black or African American	0 (0%)	1 (1.4%)	19 (17.3%)	7 (10.8%)	30 (4.8%)	57 (6.2%)
Other (including multiple)	0 (0%)	2 (2.7%)	0 (0%)	0 (0%)	19 (3.1%)	21 (2.3%)
White	0 (0%)	69 (93.2%)	88 (80.0%)	58 (89.2%)	432 (69.7%)	647 (70.9%)
Not Reported	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (1.9%)	12 (1.3%)
ETHNICITY						
Not Reported	43 (100%)	0 (0%)	1 (0.9%)	1 (1.5%)	12 (1.9%)	57 (6.2%)
Not Hispanic or Latino	0 (0%)	74 (100%)	101 (91.8%)	62 (95.4%)	556 (89.7%)	793 (87.0%)
Hispanic or Latino	0 (0%)	0 (0%)	8 (7.3%)	2 (3.1%)	52 (8.4%)	62 (6.8%)
RENAL IMPAIRMENT						
Normal	4 (9.3%)	60 (81.1%)	46 (41.8%)	25 (38.5%)	216 (34.8%)	351 (38.5%)
Mild	29 (67.4%)	14 (18.9%)	33 (30.0%)	28 (43.1%)	278 (44.8%)	382 (41.9%)
Moderate	10 (23.3%)	0 (0%)	30 (27.3%)	12 (18.5%)	123 (19.8%)	175 (19.2%)
Severe	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	3 (0.5%)	4 (0.4%)

Source: Adapted from Appendices 9.1 and 9.3 in the population PK report.

Model: Model development starts with a three-compartment disposition model with first order absorption and elimination was used to describe the relugolix concentration time-course. The model structure is shown in Figure 1. Inter-individual variability (IIV) was included on Ka, CL/F and Vc/F. Dose-normalized plots of the raw data between different treatment groups indicated slightly greater than dose proportional increase in exposure with dose, which was characterized by an effect of dose on F1. Results of the graphical exploratory covariate analysis revealed a clear trend for race effect on CL/F and Vc/F, and slight trends of age, body weight, EGFR, and CRCL on CL/F and Vc/F. All those relationships were tested one by one. Age (45 to 91 years with median 71) and body weight (40.5 to 193 kg with median 80.6) effects on CL/F and race effect (Black/African American (6.2%) vs non-Black/African American (93.8%)) on CL/F and Vc/F, and dose effect on F1, were identified as covariates in the final PopPK model. Inter-Individual variability of Ka has a high shrinkage of 70.4%. Caution should be taken when using the model estimates at the individual level. The parameter estimates are summarized in Table 3. The final model was further assessed via goodness-of-fit and visual predictive check (See Figure 2).

Figure 16. Model Structure.



Abbreviations: CL/F = apparent clearance; F1: relative bioavailability; Tlag = lag time; Ka = absorption rate constant; Q1/F = apparent intercompartmental clearance with first peripheral compartment; Q2/F = apparent intercompartmental clearance with second peripheral compartment; Vc/F = apparent volume of distribution in the central compartment; Vp1/F = apparent volume of distribution in the first peripheral compartment; Vp2/F = apparent volume of distribution in the second peripheral compartment; CEN = central compartment; PER1 = first peripheral compartment; PER2 = second peripheral compartment.

Source: Figure 5 in the population PK report.

Table 28. Parameter Estimates of Final Population PK Model.

Parameter (unit)	Estimate	SIR RSE (%) [‡]	SIR 95%CI	Shrinkage (%)
F1 (unitless)	1 (fixed)	-	-	-
Ka (1/h)	3.326	-	-	-
CL/F (L/h)	467.6	1.87	451 - 486	-
Vc/F (L)	7053	6.58	6240 - 8120	-
Vp1/F (L)	11730	-	-	-
Vp2/F (L)	14550	-	-	-
Q1/F (L/h)	16.49	-	-	-
Q2/F (L/h)	584.9	-	-	-
Lag time (h)	0.273	-	-	-
Dose ~ F1 (-) **	0.389	3.6	0.361 - 0.416	-
Age at baseline on CL/F (-) **	-0.419	22.9	-0.628 - -0.234	-
Black or African American on CL/F(-)	-0.284	17.3	-0.379 - -0.186	-
Weight at baseline on CL/F (-) **	0.322	19.5	0.197 - 0.453	-
Black or African American on Vc/F (-)	-0.681	12.8	-0.821 - -0.476	-
Inter-individual variability (IIV)				
IIV Ka (%CV)	159.9	15.1	121 - 211	70.4
IIV CL/F (%CV)	46.93	2.85	44.5 - 49.7	7.52
Correlation CL/F ~ Vc/F	70.19	-	-	-
IIV Vc/F (%CV)	122.9	4.64	112 - 134	32.9
Residual unexplained variability (RUV)				
Additive error on log scale (-)	0.404	0.681	0.399 - 0.409	5.57

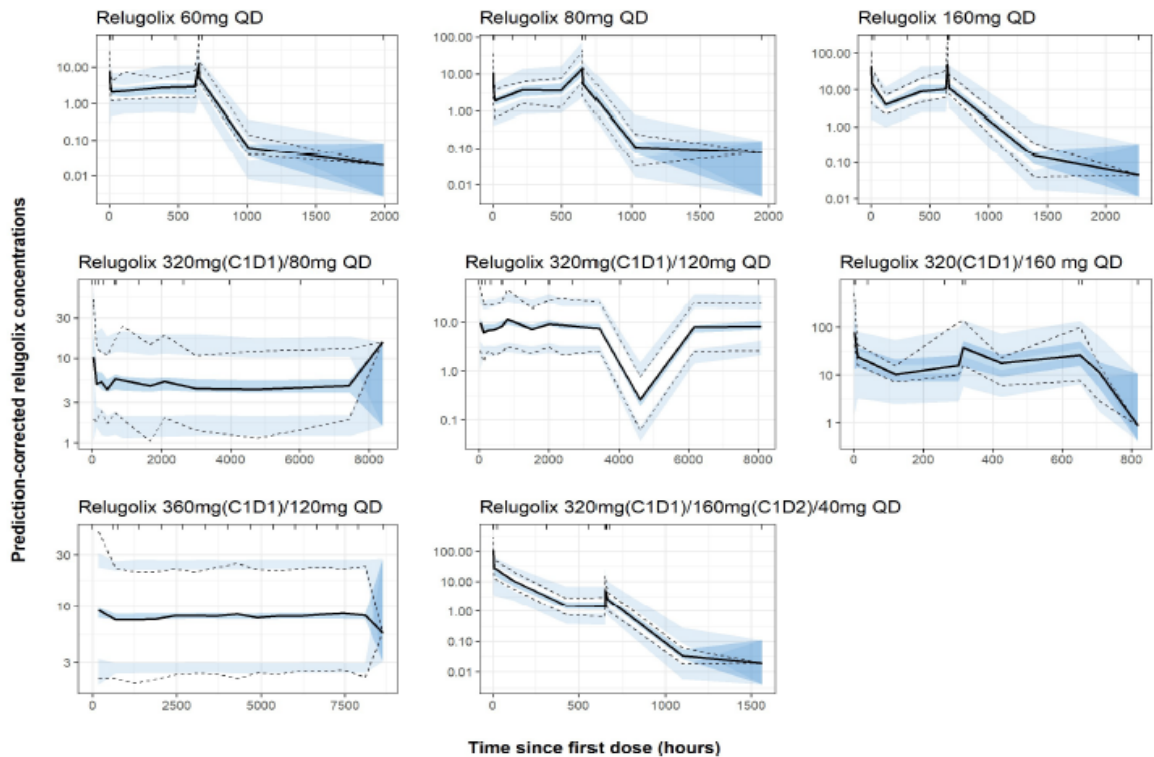
Abbreviations: CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; F1 = relative bioavailability; Ka = absorption rate constant; Q1/F = apparent intercompartmental clearance with first peripheral compartment; Q2/F = apparent intercompartmental clearance with second peripheral compartment; Vc/F = apparent volume of distribution in the central compartment; Vp1/F = apparent volume of distribution in the first peripheral compartment; Vp2/F = apparent volume of distribution in the second peripheral compartment; RSE = relative standard error; SIR = sampling importance resampling; - = unitless.

[‡]The relative standard errors for omega and sigma are reported on the approximate standard deviation scale (SE/variance estimate)².

** Covariate effects were incorporated using a power function. The typical individual is [non Black or African American] and has [weight 80.6 kg] and [age 71 years].

Source: Table 8 in the population PK report.

Figure 17. Visual Predictive Check of Final Model.



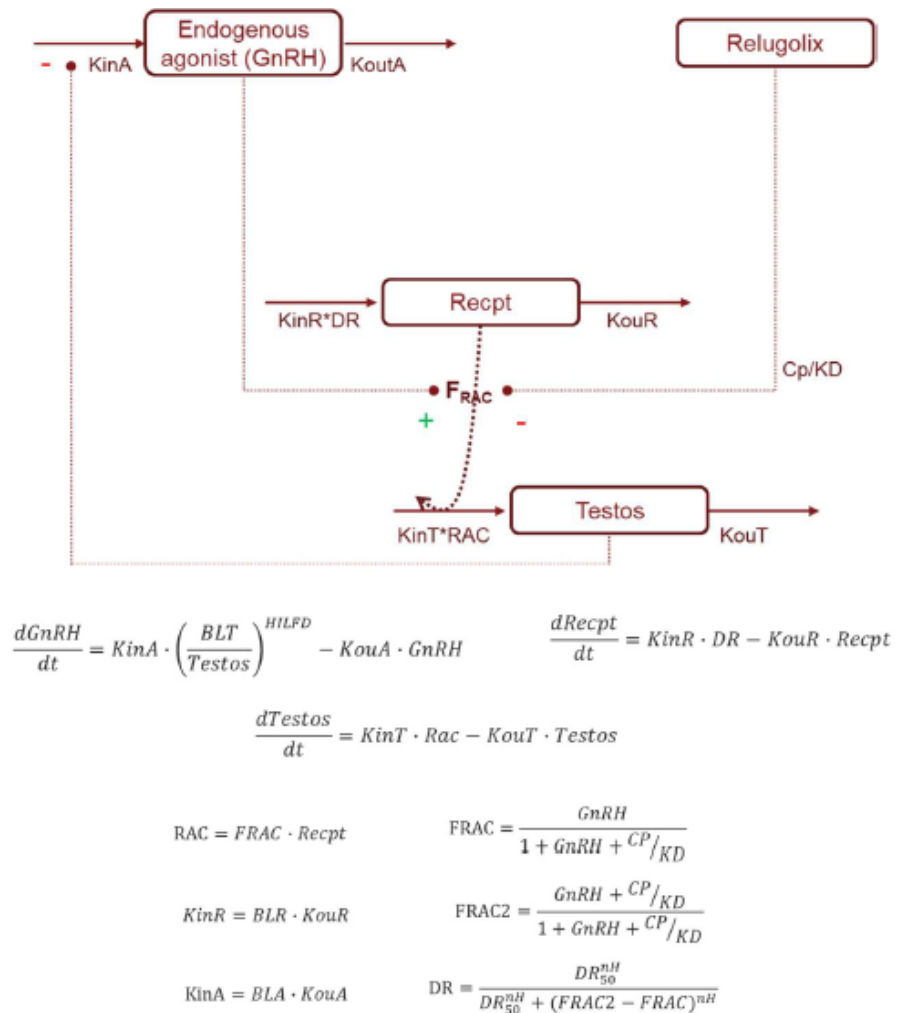
Abbreviation: C1D1 = loading dose on day 1; C1D2 = loading dose on day 2; QD = once daily
Note. The black solid and dashed lines represent median and 5-95th percentiles of the observed data, respectively. The blue shaded areas represent 90% CI of the median and 5-95th percentiles of the simulated data.

Source: Figure 8 in the population PK report.

Pharmacokinetic/pharmacodynamic analysis

Only subjects with both PK and testosterone information available in the PopPK data were kept for the analysis. Overall 13983 measurable testosterone concentrations from a total of 899 subjects were used in the PopPK/PD analysis. The PK/PD model in describes testosterone dynamics via inclusion of the main components of the Hypothalamic-Pituitary-Gonadal (HPG) axis: testosterone, GnRH receptor and the endogenous GnRH receptor agonist (GnRH). It includes production and degradation processes with competitive and reversible inhibition of endogenous GnRH binding by relugolix. Also, two feedback mechanisms were incorporated in the model: modulation (downregulation) of GnRH receptor production, driven by activation of the GnRH receptor, and testosterone-dependent production of endogenous GnRH, to enable a return to baseline testosterone levels. Inter-individual variability (IIV) was added on the testosterone production (KinT) and an additive residual error model on log scale was used. Age was included as a covariate on testosterone production. Post-hoc parameter estimates from the PopPK model were used as input for the PD model. Table 4 shows the parameter estimates for the final population PK/PD model. The model was further assessed via goodness-of-fit and visual predictive check plots (See Figure 4).

Figure 18. Schematic Representation of the Base Population PK/PD Model



Abbreviations : BLA= baseline value for the endogenous agonist compartment (GnRH); BLR = baseline value for the GnRH receptor; BLT: baseline value for testosterone; Cp=Relugolix plasma concentration; DR = receptor down regulation; DR50 = Level of receptor activation at which receptor downregulation is at 50% of maximum; FRAC= fraction of activated GnRH receptors (by agonist); FRAC2= fraction of activated GnRH receptors (by agonist and antagonist); GnRH = gonadotropin-releasing hormone (endogenous agonist); HILFD = Hill coefficient of the testosterone-feedback on GnRH production; KD = receptor equilibrium dissociation constant; KinR = zero order GnRH receptor production rate constant; KinA = zero order endogenous GnRH production rate constant; KinT = zero order testosterone production rate constant; KouA = first order endogenous GnRH degradation rate constant; KouR = GnRH receptor first order degradation rate constant; KouT = testosterone first order degradation rate constant; nH = Hill coefficient of the down regulation of GnRH receptor production; RAC = amount of activated receptors; Recept = receptor; Testos = testosterone.

Source: Figure 22 in the population PK report.

Table 29. Parameter estimated for the final PK/PD model

Parameter	Estimate	RSE(%)	CI95%	Shrinkage(%)
KinT (pg/mL/h)	640	4.03	[592 ; 691]	-
KD (pg/mL)	0.209	4.66	[0.192 ; 0.23]	-
KouT (1/h)	0.0915	3.37	[0.0858 ; 0.0979]	-
DR50 (unitless)	0.313	0.462	[0.31 ; 0.316]	-
KouR (1/h)	0.0118	1.68	[0.0114 ; 0.0122]	-
BLA (unitless)	1 (fixed)	-	-	-
nH (unitless)	7.96	1.26	[7.76 ; 8.16]	-
HILFD (unitless)	1 (fixed)	-	-	-
Age~KinT	-0.662	17.6	[-0.89 ; -0.442]	-
Interindividual Variability				
ETA KinT (CV%)	45.7	2.63	[43.5 ; 48.3]	2.8
Residual Variability				
Additive error on log scale	0.42	0.601	[0.415 ; 0.425]	3.1

Source: Table-parameters-v1.Rmd

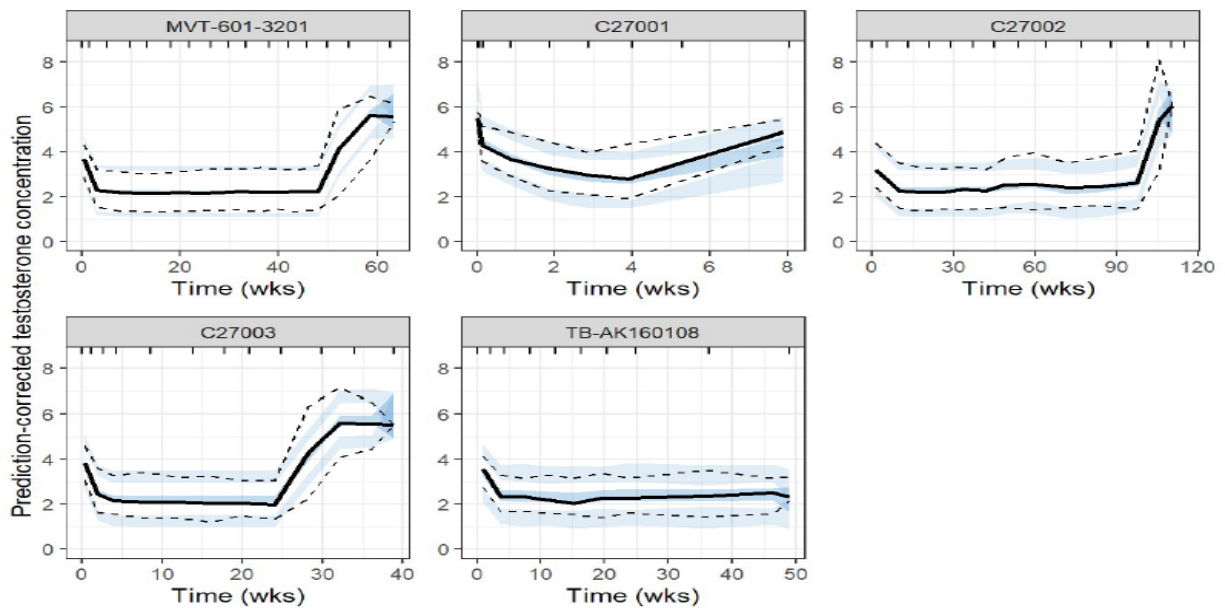
Abbreviations : BLA= baseline value for the endogenous agonist compartment; CI = confidence interval; CV = coefficient of variation; DR50 = Level of receptor activation at which receptor downregulation is at 50% of maximum; HILFD = Hill coefficient of the testosterone-feedback on GnRH production; KD = receptor equilibrium dissociation constant; KinT = zero order testosterone production rate constant; KouA = first order endogenous GnRH degradation rate constant; KouR = GnRH receptor first order degradation rate constant; KouT = testosterone first order degradation rate constant; nH = Hill coefficient of the down regulation of GnRH receptor production; RSE = relative standard error.

RSEs and 95%CIs were computed from the sampling importance resampling (SIR) process.

*The relative standard errors for inter-individual variability and residual variability parameters are reported on the approximate standard deviation scale (SE/variance estimate)/2.

Source: Table 14 in the population PK report.

Figure 19. Visual Predictive Check of the Final PK/PD Model Stratified by Study.



Source: Figure 24 in the population PK report.

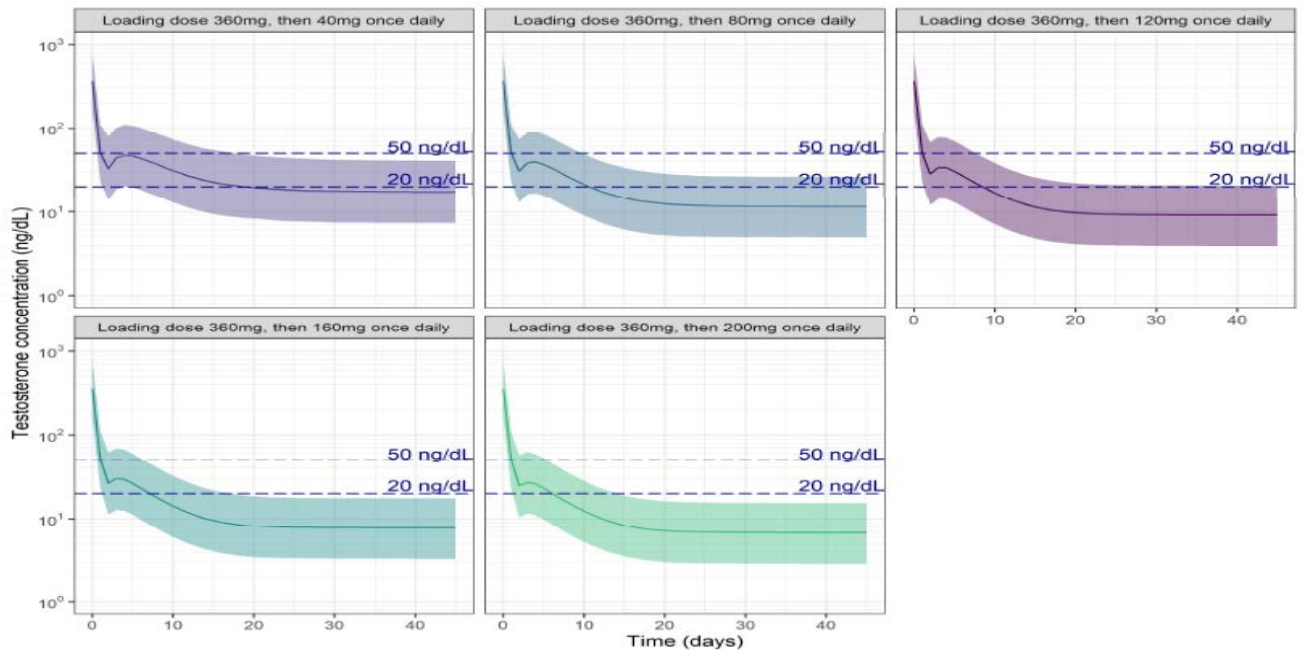
Simulations

The final PopPK/PD model was used to simulate both the relugolix and testosterone concentrations. Simulations were computed without residual variability and without uncertainty in parameter estimates. The different investigated scenarios were produced with a representative population of the phase 3 study, with a bootstrap of 1000 individuals from the MVT-601-3201 study.

Effect of Various Dosing Regimens

Testosterone response following various dosing regimens (360 mg loading dose, then 40, 80, 120, 160 or 200 mg once daily) assuming a full compliance were simulated using the final PopPK/PD model in order to explore the dose-response relationship and to support the dose selection. Figure 5 shows that the reference dosing regimen (360 mg loading dose, then 120 mg once daily) is expected to provide a testosterone suppression below the profound castrate level of < 20 ng/dL in the vast majority of patients, with the upper bound of the 90% PI approaching 20 ng/dL from approximately Day 25). Simulations also demonstrated that higher relugolix doses are unlikely to be more efficacious.

Figure 20. Simulation of the testosterone after administration of different dosing regimens.



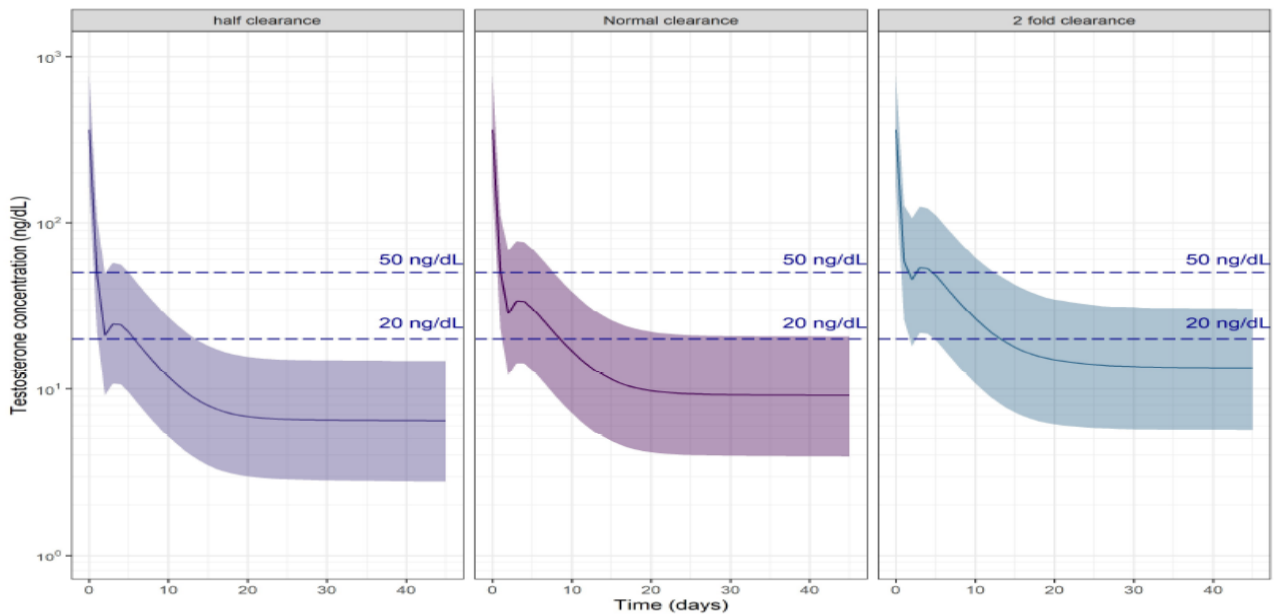
Note: The shaded area represents the 90% prediction interval of the simulations. The solid lines represent the median of the simulations. Relugolix was administered for 45 days to reach steady-state testosterone concentrations. Testosterone concentrations of < 50 ng/dL, and < 20 ng/dL represent castrate levels, and profound castrate levels.

Source: Figure 28 in the population PK report.

Impact of Clearance Increase or Decrease

Testosterone concentrations were simulated using the final PopPK/PD model while varying the apparent clearance value of relugolix (0.5-, 1- and 2-fold the estimated CL/F value of 468 L/h). Individuals were simulated under the assumption of a full compliance to the reference dosing regimen (360 mg loading dose, then 120 mg once daily). Figure 6 shows that in the case of a 2 fold increase in apparent clearance (which may occur in the case of a concomitant administration of an enzyme inducer), more than 90% of the patients are expected to reach castrate levels (< 50 ng/dL) but not the profound castrate levels (< 20 ng/dL). In addition, 2-fold increase of the apparent clearance of 468 L/h is close to the upper limit of CL/F among the subjects used to establish the final PopPK/PD model. Therefore, there will be uncertainty in the simulation results and caution should be taken when interpreting the results.

Figure 21. Simulation of testosterone concentrations at different clearance levels.



Note: The shaded area represents the 90% prediction interval of the simulations. The solid lines represent the median of the simulations.
Relugolix was administered for 45 days to reach steady-state testosterone concentrations.
Testosterone concentrations of < 50 ng/dL, and < 20 ng/dL represent the normal range, castrate levels, and profound castrate levels.

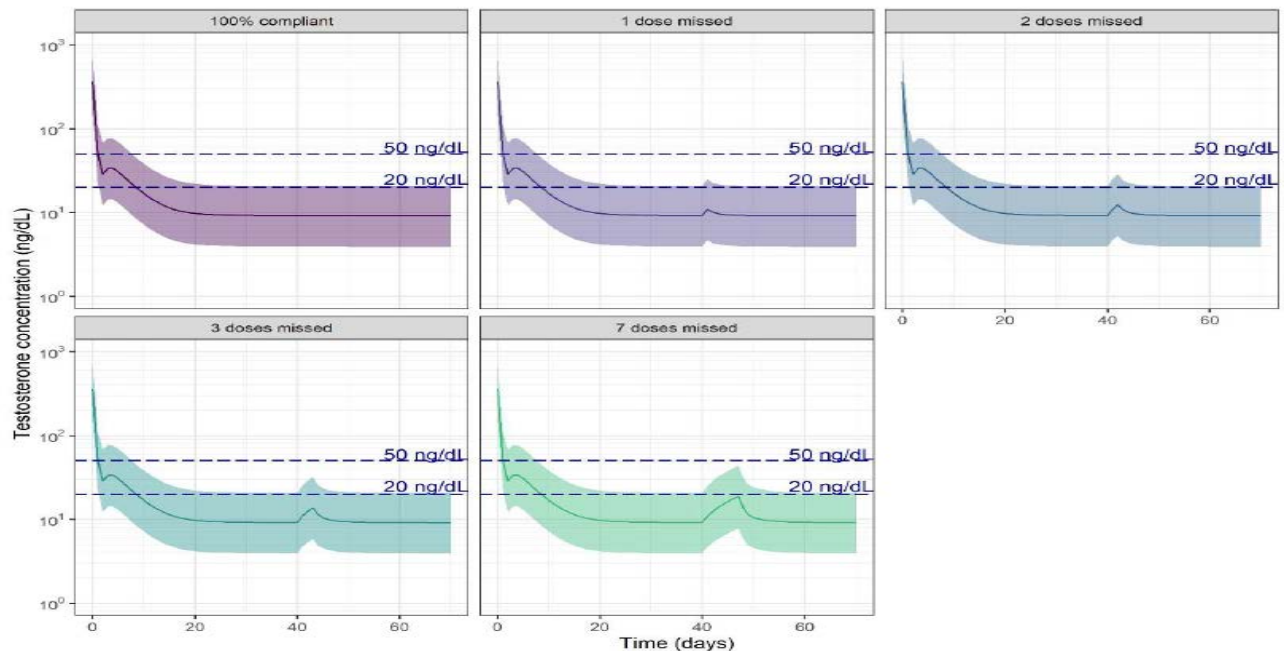
Source: Figure 30 in the population PK report.

Impact of Missing Doses and Treatment Discontinuation

Simulations were performed to investigate the impact of treatment compliance via simulations by comparing the testosterone profiles after various numbers of missed doses (1, 2, 3 and 7 missed doses) and after treatment discontinuation. For each simulated scenario, the reference dosing regimen (360 mg loading dose, 120 mg QD maintenance dose) was used, full compliance was assumed until the first missed dose,

and missed doses and treatment discontinuation were simulated at steady state (from 40 days of treatment) since maximal testosterone suppression was reached at that time (40 days). The 90% prediction interval (PI) were derived as the 5th to 95th percentile range of relevant model predictions across the 1000 simulated individuals. Figure 7 shown that testosterone levels for more than 90% of the patients still remain at castrate levels (< 50 ng/dL) even after 7 days of missed doses. The median testosterone profile recovers to above the profound castrate level (20 ng/dL) and the castrate level (50 ng/dL) after 9 and 25 days respectively, and returns to 280 ng/dL (lower end of the normal range for testosterone) after 52 days as shown in Figure 8.

Figure 22. Simulation of the Impact of Missed Doses on Testosterone Profile.



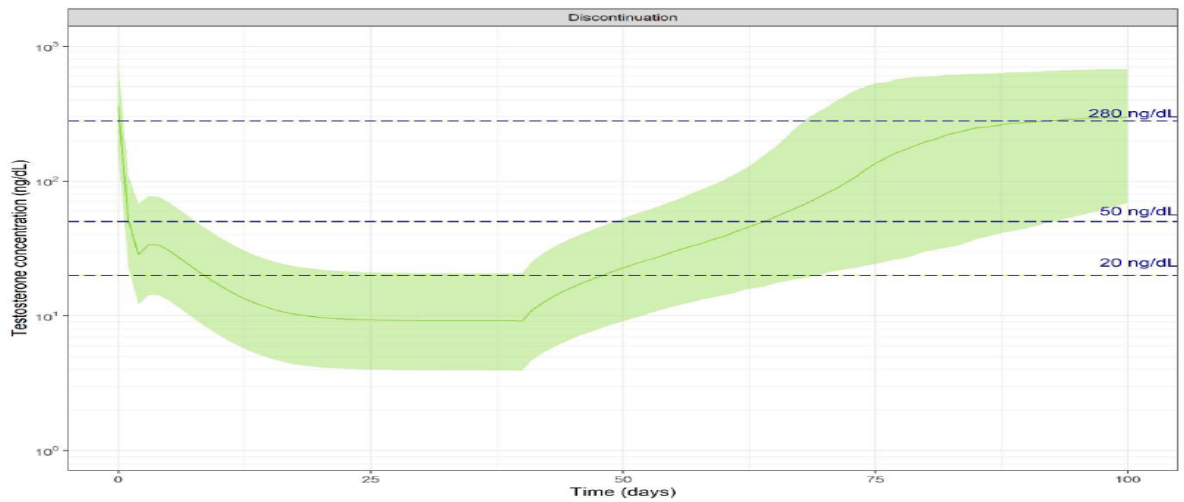
Note: The shaded area represents the 90% prediction interval of the simulations. The solid lines represent the median of the simulations.

Relugolix was administered for 40 days, followed by 1 to 7 consecutive missed doses, then dosing resumed until Day 70.

Testosterone concentrations of < 50 ng/dL, and < 20 ng/dL represent , castrate levels, and profound castrate levels.

Source: Figure 31 in the population PK report.

Figure 23. Simulation of Testosterone Profile After Treatment Discontinuation.



Notes: The shaded area represents the 90% prediction interval of the simulations. The solid line represents the median of the simulations.
Testosterone concentrations of ≥ 280 ng/dL, < 50 ng/dL, and < 20 ng/dL represent the normal range, castrate levels, and profound castrate levels.
Relugolix was administered for 40 days to reach steady-state testosterone concentrations. Treatment discontinuation started after day 40.

Source: Figure 32 in the population PK report.

Bioanalytical Method Summary

A summary of the validation data supporting the bioanalytical methods used for determination of relugolix concentrations in human plasma and urine samples from clinical studies are provided in the following table. All bioanalytical methods used for measurement of relugolix concentrations in human biomatrices were based on high performance liquid chromatography (HPLC) with electrospray ionization tandem spectrometry (HPLC-ESI-MS/MS), and are thoroughly validated.

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Clinical Study	Matrix	Method Summary	Laboratory	Assay Performance					Study Report
				LLOQ	Range	%RE ^a	%CV ^a	Validation Report	
Relugolix (TAK-385; RVT-601; MVT-601) in Human Plasma									
TAK-385_106	Plasma (sodium heparin)	LLE + LC-MS/MS	BASi	0.01 ng/mL	0.01 – 50.0 ng/mL	2.0%	6.0%	1000-071076-1 1000-071076-2 1000-071076-3 1000-071076-4	0221-13146-1
TAK-385_1009				0221-14311-1.01					
C27001				1006-11346-1					
TAK-385_1010				1006-15083-1					
C27005				1006-14034-1					
C27002	Plasma (K ₂ EDTA)			0.05 ng/mL	0.05 – 50.0 ng/mL				1006-14026-1
C27003				1006-14108-1					
TB-AK160108	Plasma (heparin sodium)	LLE + LC-MS/MS	Sumika	0.01 ng/mL	0.01 – 50 ng/mL	5.3%	9.6%	NB06232V NB07046S	NB14057D
TAK-385/CPH-010				NB12060D					
MVT-601-1002	Plasma (K ₂ EDTA)	LLE + LC-MS/MS	QPS	0.05 ng/mL	0.05 – 50.0 ng/mL	3.2%	8.3%	521-1609	521-1628
MVT-601-1003									521-1621
MVT-601-1004									521-1706
MVT-601-040									2597-1902
MVT-601-043									2597-1903A
MVT-601-044									2597-1905A
MVT-601-045									2597-1907A
MVT-601-3201									521-1714
Relugolix (TAK-385; RVT-601; MVT-601) in Human Urine									
C27001	Urine	SPE + LC-MS/MS	BASi	0.5 ng/mL	0.50 – 1000 ng/mL	-8.4%	6.3%	1000-071077-1 1000-071077-2	1006-11346-1
C27005									1006-14034-1
TAK-385/CPH-010	Urine	SPE + LC-MS/MS	Sumika	0.5 ng/mL	0.50 – 1000 ng/mL	-7.8%	3.9%	NB06234V NB06235S	NB12061D
Radiolabeled Relugolix and Metabolites in Human Matrices (non-GLP assays)									
Clinical Study	Matrix	Method Summary	Laboratory	LLOQ		Bioanalytical Study Report			
TAK-385_1009	Plasma, whole blood (total ¹⁴ C radioactivity)	AMS	Accium	Plasma: 0.03 dpm/mL	Whole blood: 0.06 dpm/mL ^b	P1260, Part 1 P1260, Part 2			
	Plasma (¹⁴ C relugolix)	HPLC-AMS	Accium	0.001329 ng equivalents/mL ^b		P1260, Part 2			
	Urine, feces (total ¹⁴ C radioactivity)	LSC	Quotient Bioresearch	Urine: 2 ng equivalents/g	Feces: 25 ng equivalents/g	TDA/25			
	Urine, feces (¹⁴ C metabolites)	HPLC-LSC	T.N. TECHNOS, Ltd	2 × the background dpm per metabolite		TAK-385-13400			

Validation summary tables for the bioanalytical methods supporting the pivotal phase 3 study MVT-601-3201 are shown below for relugolix and testosterone.

Relugolix

Relugolix:

Report Title	Validation of a Method for the Determination of RVT-601 in Human Plasma by LC-MS/MS
Study Number	QPS 521-1609
Analyte Name	RVT-601
Internal Standard (IS)	[² H ₆]-RVT-601
Analytical Method Type	LC-MS/MS
Extraction Method	Liquid-liquid
Sample Volume	100 µL
QC Concentrations	0.05, 0.15, 2, 20, and 40 ng/mL
Standard Curve Concentrations	0.05, 0.1, 0.5, 1.5, 5, 15, 45, and 50 ng/mL
Lower Limit Of Quantitation	0.05 ng/mL
Upper Limit Of Quantitation	50 ng/mL
Mean Recovery of Analyte (%)	76.3
Mean Recovery of Internal Standard (%)	NA ^a
LLOQ QC Intraday Precision Range (%CV)	3.2 to 9.9
LLOQ QC Intraday Accuracy Range (%RE)	-4.0 to 11.0
Analytical QC Intraday Precision Range (%CV)	0.6 to 3.6
Analytical QC Intraday Accuracy Range (%RE)	-8.5 to 8.7
LLOQ QC Interday Precision (%CV)	8.3
LLOQ QC Interday Accuracy (%RE)	3.2
Analytical QC Interday Precision Range (%CV)	2.2 to 3.0
Analytical QC Interday Accuracy Range (%RE)	-7.0 to 8.0
Stock Solution Stability in Methanol	101 Days at -20°C 19 Hours at Ambient Temperature
Processed Sample Stability	141 Hours at 4°C
Benchtop Stability in Plasma	23 Hours at Ambient Temperature
Freeze/Thaw Stability in Plasma	6 Cycles at -20°C and -70°C
Benchtop Stability in Whole Blood	2 Hours at Ambient Temperature 2 Hours in an Ice Bath
Long-term Storage Stability in Plasma	365 Days at -20°C 708 Days at -70°C
Dilution Integrity	100 ng/mL diluted 20-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS
2% Hemolyzed Plasma Test	No impact on assay performance
Lipemic Plasma Test	No impact on assay performance

^a Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.

Testosterone

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the Determination of Testosterone in Human Serum by HPLC with MS/MS Detection Validation Report (b) (4)		
Method description	LC-MS/MS		
Materials used for calibration curve & concentration	Analyte: testosterone Internal standard (IS): testosterone-d ₃ Surrogate matrix: phosphate buffer saline, containing 1% bovine serum albumin Concentrations for standard calibration: 20, 40, 120, 500, 1500, 4500, 9000, 10000 pg/mL		
Validated assay range	20 – 10000 pg/mL		
Material used for QCs & concentration	Analyte: testosterone IS: testosterone-d ₃ Matrix: human serum Concentrations for QC: 20, 60, 227 (endogenous testosterone), 700, 4000, 8000 pg/mL		
Minimum required dilutions (MRDs)	NA		
Source & lot of reagents (LBA)	Testosterone: (b) (4) lot number (b) (4) Testosterone-d ₃ : (b) (4) lot number (b) (4)		
Regression model & weighting	Linear regression with 1/concentration ² weighting		
Validation parameters	Method validation summary		Source location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Table 7.6
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.4 – 2.0 %	Table 7.6
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 8.1 %	Table 7.6
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 6 QCs QCs:	Intra-batch -17.5 – 11.0 % Inter-batch 1.0 – 8.0 %	Table 7.10
	Inter-batch %CV QCs:	≤ 19.8 %	Table 7.10
	Total error QCs:	NA	NA
Selectivity & matrix effect	Endogenous testosterone level in blank human serum: 8 lots of blank matrix tested; endogenous testosterone ranged in 151 – 359 pg/mL. Non-specific interference from blank surrogate matrix: blank surrogate matrix spiked with analyte at ULOQ, with IS, or with blank reagent were tested; no significant interference in the chromatographic region of interest was demonstrated. Matrix effect for IS: blank human serum from 6 lots were tested; %CV 1.9%		Table 7.5 (endogenous testosterone); Section 4.7 (non-specific interference); Section 4.12

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Relugolix

		and Table 7.15 (matrix effect)
Interference & specificity	NA	NA
Hemolysis effect	265 and 8000 pg/mL tested; bias% 4.9% and 0.5%, respectively	Table 7.18
Lipemic effect	101 and 8000 pg/mL tested; bias% 9.9% and 1.3%, respectively	Table 7.19
Dilution linearity & hook effect	80000 pg/mL diluted 20-fold; bias% 7.6%	Table 7.13
Bench-top/process stability	48 hours at room temperature in human serum or surrogate matrix; 26 hours on wet ice in human serum or surrogate matrix 146 hours at 2 – 8°C for processed samples	Table 7.27 to Table 7.30 (bench-top stability); Table 7.35 (processed sample stability)
Freeze-Thaw stability	5 cycles at -20°C or -70°C in human serum or surrogate matrix	Table 7.31 and Table 7.32
Long-term storage	At least 166 days at -20°C or -70°C in human serum or surrogate matrix	Table 7.33 and Table 7.34
Parallelism	NA	NA
Carry over	≤ 20% LLOQ for analyte and ≤ 5% IS standard for IS, with two exceptions of > 20% LLOQ for analyte. The review by the responsible scientist confirmed that the carryover observed was not significant and did not affect the integrity of the data generated.	Section 4.11 and Section 5.1
Method performance in study MVT-601-3201 (Bioanalytical Study Report (Report Number Pending))		
Assay passing rate	92.3%; incurred sample reanalysis (ISR) was performed in an on-going manner throughout the analytical phase	
Standard curve performance	<ul style="list-style-type: none"> • Cumulative bias range %: -1.8 – 1.5% • Cumulative precision (%CV): ≤ 6% 	
QC performance	<ul style="list-style-type: none"> • Cumulative bias range %: -7.1 – 7.4% • Cumulative precision (%CV): ≤ 12.4% • Total error % (LBA only): NA 	
Method reproducibility	Incurred sample reanalysis (ISR) was performed in 5% of study samples and 98.3 % of samples met the pre-specified criteria	
Study sample analysis/stability	Long-term matrix stability is established for 515 days at -20°C and -70°C in the validated method. Three samples were analyzed outside of the stability of 515 days.	

FDA considers the bioanalytical methods used in the current submission are acceptable to support the clinical pharmacology program of relugolix.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Claudia Miller	OOD/DHOT	Sections: 5	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Claudia Miller -S <small>Digitally signed by Claudia Miller -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Claudia Miller -S, 0.9.2342.19200300.100.1.1=2002180206 Date: 2020.12.16 14:05:28 -05'00'</small>			
Nonclinical Team Leader	Tiffany Ricks	OOD/DHOT	Sections: 5	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Tiffany K. Ricks -S <small>Digitally signed by Tiffany K. Ricks -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000497170, cn=Tiffany K. Ricks -S Date: 2020.12.16 12:33:53 -05'00'</small>			
Nonclinical Team Division Director	John Leighton	OOD/DHOT	Sections: 5	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
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Clinical Pharmacology Reviewer	Yibo Wang	OTS/OCP/DCP I	Sections: 6, 19.4	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
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Clinical Pharmacology Team Leader	Pengfei Song	OTS/OCP/DCP II	Sections: 6, 19.4	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
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Clinical Pharmacology Division Director	Nam Atiqur Rahman	OTS/OCP/DCP II	Sections: 6, 19.4	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
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Pharmacometrics Reviewer	Junshan Qiu	OTS/OCP/DPM	Sections: 6, 19.4	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
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Pharmacometrics Team Leader	Jingyu (Jerry) Yu	OTS/OCP/DPM	Sections: 6, 19.4	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
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Clinical Reviewer	Mehrnoosh Hadadi	OOD/DO1	Sections: 2, 3, 4, 7, 8, 10, 11, 19.1, 19.2, 19.5	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Mehrnoosh Hadadi -S <small>Digitally signed by Mehrnoosh Hadadi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002917026, cn=Mehrnoosh Hadadi -S Date: 2020.12.16 13:08:32 -05'00'</small>			
Clinical Reviewer	Sundee Agrawal	OOD/DO1	Sections: 2, 3, 4, 7, 8, 10, 11, 19.1, 19.2	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
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Biostatistics Reviewer	Lijun Zhang	OTS/OB/DBV	Sections: 1,8	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
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Biostatistics Team Leader	Mallorie Fiero	OTS/OB/DBV	Sections: 1, 8	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
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Division Director (OB)	Shenghui Tang	OTS/OB/DBV	Sections: 1,8	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
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Associate Director of Labeling (ADL)	William Pierce	OCE/OOD	Sections: 11, Prescribing Information, Patient Labeling	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
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Cross-Disciplinary Team Leader (CDTL)	Daniel Suzman	OOD/DO1	Sections: Authored 1/Approved All	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Daniel L. Suzman -S <small>Digitally signed by Daniel L. Suzman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011281337, cn=Daniel L. Suzman -S Date: 2020.12.16 12:38:20 -05'00'</small>			
Division Director (Clinical)	Amna Ibrahim	OOD/DO1	Sections: All	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Amna Ibrahim -S <small>Digitally signed by Amna Ibrahim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amna Ibrahim -S, 0.9.2342.19200300.100.1.1=1300150984 Date: 2020.12.16 16:19:33 -05'00'</small>			

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Office Director (Clinical)	Paul Kluetz	OOD	Sections: All	Select one: ___ Authored <u>X</u> Approved
	Signature: See the electronic archive for signature.			

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