EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2022
EMA/218094/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orgovyx

International non-proprietary name: relugolix

Procedure No. EMEA/H/C/005353/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ADME	absorption, distribution, metabolism, elimination
ADT	androgen deprivation therapy
ALT	alanine aminotransferase
AMS	Aging Males Symptoms
ARA	acid-reducing agent
ASR	age-standardised rate
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC0-?	area under the concentration-time curve from time zero extrapolated to infinity
AUC0-?	area under the concentration-time curve from time zero to tau
AUCss	area under the concentration-time curve at steady state
BCRP	breast cancer resistance protein
BMI	body mass index
CFU	Colony stimulating factor
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLcr	creatinine clearance
Cmax	maximum observed concentration
CPPs	critical process parameters
CRFS	castration resistance free survival
CSR	clinical study report
Ctrough	trough concentration
Ctrough-SS	trough concentration at steady state
CYP	cytochrome P450
ddQTcF	time-matched post-dose mean difference in baseline- and placebo-adjusted QTc interval with Fridericia correction (double delta QTcF)
DEPT-135	Distortions Enhancement by Polarization Transfer
DHT	dihydrotestosterone
DOE	design of experiment
DQF-COSY	Double-Quantum Filtered Correlation Spectroscopy
EAU	European Association of Urology
EBRT	external beam radiation therapy

ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
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
EPAR	European public assessment report
EQ 5D 5L	EuroQol 5-Dimension 5-Level Scale
ESMO	European Society for Medical Oncology
EU	Europe(an)
F	absolute bioavailability
FDA	Food and Drug Administration (US)
FMEA	failure mode effect analysis
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMR	geometric mean ratio
GnRH	gonadotropin-releasing hormone
HbA1c	haemoglobin A1c
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High performance liquid chromatography
HR	hazard ratio
ICH	International Council for Harmonisation
IR	infra-red spectroscopy
Km	in vitro P-gp affinity constant
LC/MS	liquid chromatography/mass spectrometry
LCMS	Liquid chromatography–mass spectrometry;
LDPE	low-density polyethylene
LH	luteinizing hormone
MA(A)	Marketing Authorisation (Application)
MACE	major adverse cardiovascular event

MDRD	modified diet restricted in diabetes
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NA	not applicable
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NMR	Nuclear magnetic resonance spectroscopy
NR	not reached
OATP	organic anion-transporting polypeptide
OS	overall survival
PC	prostate cancer
PCWG3	Prostate Cancer Working Group 3
PD	pharmacodynamic
P-gp	P-glycoprotein
Ph.	Eur. European Pharmacopoeia
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PopPK	population pharmacokinetic
PopPK/PD	population pharmacokinetic/pharmacodynamic
PSA	prostate-specific antigen
PXRD	Powder X-ray diffraction
QbD	Quality by design
QD	once daily
QTc	QT interval corrected for heart rate
QTPP	quality target product profile
RT	Retention time
SA	Scientific Advice
SAP	statistical analysis plan
SAWP	Scientific Advice Working Party
SD	standard deviation
SHBG	sex hormone binding globulin
SmPC	Summary of Product Characteristics
SMQ	Standardised Medical Dictionary for Regulatory Activities query

tmax	time to maximum observed concentration
UK	United Kingdom
ULN	upper limit of normal
US	United States
USP-NF	United States Pharmacopoeia – National Formulary
UV/Vis	Ultraviolet/visible
VAS	visual analog scale
Vss	volume of distribution at steady state
Vz	true volume of distribution
Vz/F	apparent volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Myovant Sciences Ireland Limited submitted on 8 March 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Orgovyx, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2019.

The applicant applied for the following indication:

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/001/2015 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
19/11/2015	EMEA/H/SAH/055/1/2015/II	*Dr Paolo Foggi, Dr João Oliveira*

The Scientific advice pertained to the following clinical aspects, and was structured as a parallel consultation with HTA bodies:

- Acceptability of the general design elements for study TAK-385-3006, including:

- study population, as defined by inclusion/exclusion criteria, to support the claimed indication
- choice of leuprorelin as comparator
- choice of primary and secondary endpoints and associated statistical analysis methods,
- dose selection

- Adequacy of the performed clinical pharmacology studies
- Adequacy of the overall safety database and monitoring plans for phospholipidosis
- Overall acceptability of the development programme to support a MA application
- Possibility of including phase 2 study results in section SmPC section 5.1
- Adequacy of the health-related quality of life assessments, and related methodology, to support B/R definition and inclusion in the SmPC

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	8 March 2021
The procedure started on	25 March 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 June 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 June 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 June 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 July 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 October 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 November 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	2 December 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	16 December 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 January 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 February 2022

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Orgovyx on	24 February 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applied indication for Orgovyx (relugolix) is:

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

'Advanced' prostate cancer is generally regarded to be cancer that has spread from the prostate to other parts of the body, i.e. metastasized disease (including non-regional lymph node metastasis), and that is beyond curation. 'Locally advanced' prostate cancer, in contrast, is defined as 'cT3-4 or cN+', i.e. disease where the tumour extends through the prostatic capsule (T3) or is fixed or invades adjacent structures other than seminal vesicles (T4); and disease with regional lymph node metastasis (N+). Patients with locally advanced prostate cancer normally are treated with curative intent (2021 EAU Guidelines on prostate cancer; 2020 ESMO Prostate cancer guidelines).

2.1.2. Epidemiology and risk factors, screening tools/prevention

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). While prostate cancer remains largely a disease diagnosed in men over 65 years of age, screening (based on serum levels of prostate-specific antigen [PSA]) has increased the rate of diagnosis among men in their 40s and 50s (Kimura and Egawa 2018).

Genetic and acquired factors (age, ethnicity, and possibly dietary) are the most important known prostate cancer risk factors (Rawla 2019). Overall survival rates in localized disease are very high, but these rates decrease dramatically for advanced and metastatic disease, with a 5-year survival rate ranging 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 increase with time, including skeletal-related events such as spinal cord compression, vertebral collapse, and pathological fractures (Auclerc et al. 2000; McMurtry and McMurtry 2003). Furthermore, patients with advanced prostate cancer are at a significantly higher risk of cardiovascular disease than men of the same age without prostate cancer (Keating et al. 2010a; Moustsen et al. 2019). Patients with prostate cancer without androgen deprivation therapy (ADT) exposure have a baseline higher risk of developing cardiovascular disease and this risk has been shown to increase with the use of GnRH receptor agonists (Keating et al. 2010b). Improvement in treatment and earlier diagnosis with PSA testing have resulted in fewer patients dying from prostate cancer and instead, patients with prostate cancer have a higher risk of non-cancer related mortality. Cardiovascular disease is the most common non cancer cause of death for men with prostate cancer (Satariano et al. 1998; Bhatia et al. 2016).

2.1.3. Biologic features

Already in 1941, Huggins and Hodges proposed that prostate cancer growth was driven by androgens after observing the benefits of castration in men with prostate cancer (Huggins et al. 1941). Today, evidence-based treatment guidelines recommend androgen deprivation therapy (ADT) with medical castration for the treatment of patients with prostate cancer if they are deemed to have advanced disease, are at significant risk of progressive disease and/or death, or in combination with radiotherapy

for intermediate- or high-risk localized disease (Parker et al. 2015; Mottet et al. 2017; Mohler and Antonarakis 2019).

Understanding the physiologic control of testosterone secretion is the basis for the justification of the use of GnRH receptor agonists or antagonists to cause medical androgen deprivation.

Endogenous GnRH secreted from the hypothalamus binds to GnRH receptors located on gonadotropin neurons in the anterior pituitary, stimulating synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. Both LH and FSH act on receptors in the testes. Luteinizing hormone acts on the Leydig cells to increase testosterone production from cholesterol. Testosterone self-regulates its secretion by providing negative feedback. High testosterone concentrations in the blood lead the hypothalamus to suppress GnRH secretion and make the anterior pituitary less responsive to stimulation by GnRH.

When the GnRH pathway was initially discovered, development of an antagonist proved difficult (Crawford and Hou 2009). GnRH agonists (e.g., leuprolide) became the mainstay of medical androgen deprivation once it was understood that chronic stimulation of the pathway resulted in desensitization and down regulation of the LH gonadal axis (Mcleod 2003; Sharifi et al. 2005). Therefore, GnRH agonists initially stimulate the release of LH and FSH. Continuous stimulation leads to desensitization and subsequent suppression of LH and, to a lesser extent, FSH release. The decrease in LH results in a marked reduction of systemic testosterone concentrations.

One major disadvantage of using an agonist to suppress testosterone is the initial stimulation (flare) of the hypothalamic-pituitary-gonadal axis that occurs prior to desensitization, lasting 1 to 3 weeks. This results in a rise in LH, a testosterone surge and, in some patients, an increase in clinical symptoms including bone pain, spinal cord compression, pathologic fracture, bladder outlet obstruction, and even death (Oh et al. 2010; Eligard USPI 2019; Eligard SmPC 2020). Estimated rates of clinical disease flare associated with GnRH receptor agonists range between 4% and 63% (Mahler 1993; Bubley 2001). The initial clinical flare response may be managed with simultaneous antiandrogen administration, such as bicalutamide (Thompson 2001), often called combined androgen blockade. However, use of bicalutamide has been associated with hepatotoxicity (requiring monitoring of serum transaminase levels) and gynecomastia (Casodex SmPC 2020; Casodex USPI 2017).

Men with prostate cancer have a baseline higher risk of developing cardiovascular disease, and this risk increases with the use of GnRH receptor agonists (Keating et al. 2010b). Studies have also found a higher risk of major cardiovascular events in patients with prostate cancer treated with GnRH receptor agonists compared with GnRH receptor antagonists, particularly in men with pre-existing cardiovascular disease (Saigal et al. 2007; Margel et al. 2019), and a multidisciplinary task force that provided scientific advice on the topic (Levine et al. 2010).

Degarelix (Firmagon) is currently the only GnRH antagonist approved for the treatment of prostate cancer. Degarelix, administered by monthly depot injection, achieves medical castration and a PSA response within the first 1 to 2 weeks of administration with no initial agonist activity and no clinical flare (Firmagon SmPC; Firmagon USPI 2020), and therefore, does not require combined androgen blockade. Use of degarelix in the clinical setting has been limited likely due to the rate of injection site reactions (44%) with monthly injections, which is significantly higher than that with leuprolide (< 1%) administered every 3 to 6 months (Sciarra et al. 2016). Degarelix requires a large injection volume (4 mL) compared with leuprolide (0.375 mL for the 22.5 mg 3 month depot injection) (Doehn 2009). Regarding cardiovascular risks, the Firmagon SmPC carries a general warning and precaution for cardiovascular risk associated with androgen deprivation therapy without specific cardiovascular risk associated with degarelix (Firmagon SmPC).

Current androgen deprivation therapy (ADT) options, including GnRH receptor agonists and degarelix, are only available in injectable depot formulations and testosterone suppression 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 concentrations to greater than castrate levels are highly variable and can depend on a number of factors, including ADT duration and the patient's age (Bong et al. 2008). Persistently low testosterone concentrations are associated with a wide variety of adverse events, and an additional disadvantage of this protracted or even failed return of testosterone concentrations to above castrate levels with injectable depot formulations, is the inability to stop the treatment effect rapidly.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Clinical manifestations of prostate cancer are frequently absent at the time of diagnosis. The clinical behaviour of prostate cancer ranges from a screen detected asymptomatic, microscopic, well differentiated tumour that may never become clinically significant to the rarer screen detected or clinically symptomatic aggressive, high-grade cancer that causes metastases, morbidity, and death. At the time of diagnosis, 78 percent of patients have localized cancer, regional lymph node involvement is present in 12 percent, and 6 percent have distant metastases (UpToDate, accessed 12-Apr-2021).

Population-based PSA screening of men for prostate cancer reduces prostate cancer mortality at the expense of overdiagnosis and overtreatment and is not recommended (2020 ESMO Prostate cancer guidelines).

2.1.5. Management

If prostate cancer is diagnosed at a stage where it is confined to the prostate gland, it is generally treated by active surveillance, surgical prostatectomy, or with radiation. Often, prostatectomy or radiation is successful in curing men of their disease (Widmark et al. 2009; Bill-Axelson et al. 2011; Warde et al. 2011). Men whose disease progresses after prostatectomy or radiation are defined as having advanced prostate cancer. In the past, advanced prostate cancer was defined as disease that has metastasized beyond the prostate and pelvic lymph nodes and was considered incurable (Crawford 1994). Accumulated research and evidence have expanded the definition of advanced prostate cancer to encompass patients with significant risk of disease progression and/or death (Moul et al. 2000; D'Amico et al. 2003). Prostate-specific antigen relapse represents the earliest sign of advanced disease and is an indication of residual tumour (Yu et al. 1995; Pound et al. 1997). Approximately 40% of men who receive localized treatment will experience PSA relapse, or rising PSA levels after initial therapy, and represent the most common form of advanced prostate cancer (Moul 2000; Moul et al. 2002, 2004).

ADT with radiotherapy is established as an appropriate and effective treatment option for most men with newly diagnosed intermediate- and high-risk prostate cancer (NCCN 2020). Both the European and United States (US) 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).

ADT is the foundational therapy for the treatment of patients with advanced prostate cancer (Parker et al. 2015; Attard et al. 2016). Additionally, when there is progression of the disease, 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 non-metastatic and metastatic castration-resistant prostate cancer (Mohler and Antonarakis 2019).

Current, standard of care treatment with GnRH receptor agonists has known limitations, including an initial surge in testosterone with risk of clinical flare, increased risk of cardiovascular events, injection site reactions, and slow recovery of testosterone after discontinuation of treatment (depot formulation), among others. An injectable GnRH antagonist, degarelix, is approved for use but is only available as a monthly depot injection and is associated with a high frequency of injection site reactions and slow recovery of testosterone after discontinuation of treatment. Therefore, there is a need for improved treatment options for prostate cancer. Relugolix (previously known as TAK-385, T-1331285, RVT-601, and MVT-601) is the first oral, nonpeptide, GnRH receptor antagonist developed for the treatment of patients with advanced prostate cancer. It has, indeed, been stated in scientific literature that the potential benefits of a daily-dosed oral agent could be multiple: ADT without an injectable depot (1) offers a more patient-friendly alternative with limited health care provider visits or procedures and no risk of local site reactions; (2) allows more flexible dosing and an option for prompt cessation of treatment due to intolerance or treatment-related side effects; and (3) eliminates the need for a lead-in antiandrogen to counteract potential testosterone flare induced with LHRH agonist-based treatments (Sachdev et al. Eur Urol. 2020). However, oral ADT is not without its own drawbacks. Depot formulation can offer reliable, sustained plasma delivery without reliance on patient adherence, interactions with other oral medications, or gastrointestinal absorption. The bothersome side-effect profile of ADT may lead to earlier cessation or interruption of oral therapy by patients. Furthermore, while in studies good adherence to oral dosing of medications may be shown, real-life compliance to long-term daily dosing is likely to be less optimal. Lastly, it is unclear if more rapid testosterone recovery would make the drug effect of the same nominal duration as in trials using GnRH agonist depot injection-based treatment (Sachdev et al. Eur Urol. 2020), and a shorter duration of testosterone suppression with relugolix (due to faster testosterone recovery) could lead to undertreatment given that cancer control has been associated with the duration of testosterone suppression (Mahal et al. Eur Urol. 2020). In conclusion, whereas there is perhaps not a high unmet medical need for an oral formulation of a GnRH receptor agonist, it can be considered a valuable addition to the treatment armamentarium for advanced hormone-dependent prostate cancer.

2.2. About the product

Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to GnRH receptors in the anterior pituitary preventing native GnRH receptors from binding and signalling the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Consequently, the production of testosterone from the testes is reduced.

The initially applied indication was:

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

The finally approved indication was:

Orgovyx is indicated for the treatment of adult patients with advanced hormone-sensitive prostate cancer.

Treatment with Orgovyx should be initiated with a loading dose of 360 mg (three tablets) on the first day, followed by a 120 mg (one tablet) dose taken once daily (QD) at approximately the same time each day.

2.3. Type of Application and aspects on development

The clinical development of relugolix (monotherapy) for the treatment of patients with advanced prostate cancer includes 17 studies conducted in healthy participants, patients with hepatic or renal impairment, patients with advanced prostate cancer, and patients with intermediate-risk localized disease in combination with radiotherapy. All clinical studies key to the development of relugolix for the treatment of patients with advanced prostate cancer are shown in Table 1.

Table 1. Overview of Relugolix Clinical Development Program for Patients with Prostate Cancer Eligible for Androgen Deprivation Therapy

Phase 1 Studies	Phase 2 Studies	Phase 3 Study
Dose-Range-Finding Study in Nonmetastatic Prostate Cancer TB-AK160108	**ADT in Advanced Prostate Cancer** C27002	**ADT in Advanced Prostate Cancer** MVT-601-3201
Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study C27001	**Neoadjuvant/adjuvant ADT Therapy to External Beam Radiotherapy** C27003	
Bioavailability and Food Effects Study TAK-385-1010		
Drug-Drug Interaction Studies Erythromycin (Strong P-gp/moderate CYP3A4 inhibitor) TAK-385/CPH-010 Atorvastatin and Fluconazole (Weak and moderate CYP3A4 inhibitors) C27005 Rifampin (Combined P-gp and strong CYP inducer) MVT-601-1004 Voriconazole (Strong CYP3A4 inhibitor) MVT-601-043 Midazolam (CYP3A4 substrate) MVT-601-044 Rosuvastatin (BCRP substrate) MVT-601-045		
Human ADME and Absolute Bioavailability Study TAK-385-1009		
Mild and Moderate Hepatic Impairment Study MVT-601-1002		
Moderate and Severe Renal Impairment Studies MVT-601-1003 MVT-601-040		
Thorough QT/QTc Study TAK-385-106		

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; ADT = androgen deprivation therapy; BCRP = breast cancer resistance protein; CYP = cytochrome P450; P--gp = P-glycoprotein; QTc = QT interval corrected for heart rate; TAK = Takeda-.

The Applicant received Scientific Advice (SA) from the Committee for Medicinal Products for Human Use (CHMP), as part of an early multi-stakeholder, parallel SA (EMA/CHMP/SAWP/742698/2015; Procedure No.: EMEA/H/SAH/055/1/2015/II). The Applicant sought advice on the design of the phase 3 registration study MVT-601-3201 (but at the time referred to as TAK-385-3006) for relugolix for the treatment of patients with hormone-sensitive advanced prostate cancer, as well as on the adequacy of the overall clinical development and clinical pharmacology plans to support a full MAA for relugolix. In general, the EMA was supportive of the proposed study design for study MVT-601-3201 as outlined at the time.

Chapter 2 of Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man contains condition-specific guidance on prostate cancer (EMA/CHMP/703715/2012 Rev. 2). In the section on therapy for metastatic disease (hormone-naïve), it is stated that for medicinal products aiming at achieving medical castration, it is sufficient to convincingly demonstrate the achievement and maintenance of castrate levels of testosterone in the absence of breakthroughs and micro-surges. It is also stated that if the aim is to achieve "surgical level" of castration, 20 ng/dL and below, clinical benefit should be demonstrated in a randomized trial vs. standard therapy (target 50 ng/dL and below) if the benefit of a lower serum testosterone target level cannot be demonstrated by other means.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a film-coated tablet containing 120 mg relugolix as active substance.

Other ingredients are: mannitol (E421), sodium starch glycolate (E468), hydroxypropyl cellulose (E463), magnesium stearate (E572), hypromellose (E464), titanium dioxide (E171), iron oxide red (E172) and carnauba wax (E903).

The product is available in bottles. Each high-density polyethylene (HDPE) bottle contains 30 film-coated tablets and a desiccant and is closed with a child-resistant induction seal polypropylene (PP) cap, as described in section 6.5 of the SmPC.

2.4.2. Active substance – Relugolix-

General information

The chemical name of relugolix is *N*-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethyl-amino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-6-yl}phenyl)-*N*'-methoxyurea corresponding to the molecular formula $C_{29}H_{27}F_2N_7O_5S$. It has a molecular mass of 623.63 g/mol and the following structure, shown in Figure 1:

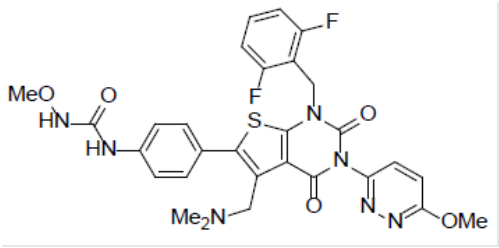


Figure 1: relugolix structure

The chemical structure of relugolix was elucidated by a combination of infra-red spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) including 1D (^{1}H-NMR, ^{13}C-NMR and DEPT-135) analysis and 2D (HMQC, DQF-COSY and HMBC) analysis, mass spectrometry, X-ray powder and single crystal diffractometry, as well as UV/Vis spectroscopy.

The active substance is a white to off-white to slightly yellow solid; the solubility of relugolix decreases with an increase of pH and it is considered a BCS IV Class compound.

Relugolix is slightly hygroscopic and requires no special protection from humidity during handling, shipping, or storage.

Relugolix exhibits polymorphism. The results of polymorph screening study showed that relugolix has several solid forms. The form selected for development and commercial use is thermodynamically the most stable form under the conditions of manufacture and storage. The polymorphic forms of relugolix can be distinguished by XRPD and the proposed manufacturing process is capable of consistently producing the desired polymorph of relugolix. Relugolix is non-chiral molecule and does not contain E/Z-isomerism.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided and it was considered satisfactory.

The manufacturing process consists of several synthetic steps and a purification by crystallisation step.

The proposed sites manufacturing the active substance use identical routes of synthesis. The starting materials are acceptable and are controlled by suitable specifications. The intermediates are sufficiently controlled. In addition, acceptable specifications for reagents, solvents and other materials used in the synthesis have been provided, including a limit for a named impurity, as part of the control strategy for nitrosamines, as described under product specification of the finished product.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The information presented regarding potential impurities/degradation products controlled in the active substance is adequate. Overall, the defined control strategy is satisfactory.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment and design of experiment (DOE) studies. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and critical process parameters (CPPs) that may have an influence on the active substance quality attributes. The risk identification was based on the process knowledge and sound scientific judgement. No design space has been claimed. The CPPs have been adequately identified and the critical steps of the process were identified and are controlled by justified and appropriate in-process controls.

Relugolix is packed in two sealed, low-density polyethylene (LDPE) bags; desiccant may be placed outside the primary packaging. Then, the double-LDPE bagged material is placed in either an aluminum-laminated bag before packaging in a secondary container or an aluminum-lined fibre drum or equivalent secondary container. The primary packing material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC, UV), particle size (laser light diffraction), assay (HPLC), impurities (HPLC), residue on ignition (Ph. Eur.), residual solvents (GC) and water content (Ph. Eur.).

The specification limits for impurities/degradation products and residual solvents, are in accordance with the requirements of ICH guidelines Q3A and Q3C. All solvents used throughout the entire

synthetic process, including those employed prior to the starting material, are routinely controlled in the specification and specified at levels in-line with the ICH Q3C thresholds.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data from three registration batches, ten process validation batches, pilot-scale, GMP, and engineering batches are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three primary batches of active substance from the proposed manufacturers stored for up to 36 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, crystal form (PXRD), identification by IR, identification by UV, related substance, water and assay. Storage at the accelerated stability condition, up to 6 months, showed no change for the same stability-indicating and quality parameters. Slight increases in two specified impurities were observed but the results remain conform. The total related substances values remained below the specification limit and all tested parameters were within the specifications.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. During exposure, the active substance becomes yellowish white. There is also an increase in unspecified related substances and total related substances. These changes are not observed during long-term or accelerated stability conditions. Based on the results, the active substance is packaged in an aluminum-laminated bag or aluminum-lined fiber drums that prevents exposure to light.

In addition, stressed stability studies were conducted for related substances on samples of relugolix active substance from one manufacture exposed to 50°C, 60°C, and 25°C/93% RH storage conditions and durations for up to 3 months, 2 months, and 3 months, respectively. The related substances method was shown to be stability indicating. There was no degradation observed in relugolix active substance.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months stored in the proposed packaging without storage restriction.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

Orgovyx (REL) 120 mg tablets are light red, almond-shaped, film-coated, immediate-release tablets debossed with "R" on one side and "120" on the other side. The dimension of the tablet is approximate 10.7 mm x 7.5 mm.

The finished product is indicated for use in male adults (18 years and older). No special considerations regarding use in the paediatric population (e.g. size of capsules, palatability,) are necessary. No overage is used.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards with the exception of iron oxide red which complies with USP-NF. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

Pharmaceutical development of the finished product contains QbD elements. The quality target product profile (QTPP) was defined as an immediate release product designed to disintegrate and dissolve rapidly under the physiological conditions in the stomach, that meets compendial and other relevant quality standards. The QTPP was based on formulation developed for clinical studies, manufacturing process considerations and the properties of the active substance; QTPP and the critical quality attributes have been described.

The formulation development has been provided with regards to selection of excipients and proposed amounts. The relugolix active substance solid form selected for clinical and commercial manufacturing of the film-coated tablets is thermodynamically stable. The particle size distribution of the active substance used in the development phase of the finished product is used for the commercial product.

The formulation used during the pivotal Phase 3 clinical studies is the same as that intended for marketing.

The discriminatory power of the QC dissolution method was demonstrated. The manufacturing development has been evaluated through the use of risk assessment and design of experiments to identify the critical process parameters and areas of process optimisation. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. Based on these experiments, process target values and acceptable ranges were established. No design space is claimed. The critical process parameters have been adequately identified.

The finished product is packaged in high density polyethylene (HDPE) bottles with desiccant and a polypropylene (PP) child-resistant induction seal cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process has been described. The process is considered to be a standard manufacturing process. Storage times of intermediates during the manufacturing process are declared and acceptable.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), identification (UV and HPLC), assay (HPLC), related substances (HPLC), dissolution (Ph. Eur.), content uniformity (Ph. Eur.), water content (Karl-Fisher, Ph. Eur.) and microbial quality (Ph. Eur.).

The proposed limits for specified impurities, as well as unspecified impurities are in-line with ICH Q3B and acceptable. Impurities controlled above the ICH qualification threshold and were qualified. The

proposed impurity levels in the finished product are acceptable from a safety point of view and process capabilities.

The limit for dissolution is in line with the general considerations in the Reflection Paper (RP) on the Dissolution Specification for Generic Solid Oral Immediate Release Products with Systemic Action (EMA/CHMP/CVMP/QWP/336031/2017) and is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). To evaluate the nitrosamine risk in the finished product upon storage, a screening of nitrosamines was conducted. In view of the indication, the finished product falls within the scope of ICH S9, hence, nitrosamine impurities should be controlled according to ICH Q3A(R2) and ICH Q3B(R2) guidelines. Taking into consideration that NDMA was detected below 10% of the acceptable intake for NDMA, absence of nitrosamines is considered adequately demonstrated.

Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The finished product is released on the market based on the release specifications, through traditional final product release testing

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for five commercial scale batches of the finished product confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from commercial scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 65% RH) for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in line with the shelf-life specifications. The analytical procedures used are stability indicating. The finished product is generally very stable when stored in the proposed container closure system and no general trends or signs of degradation are observable. No change in dissolution, water content and assay is noticed for the time-frame covered so far under all storage conditions. The

stability of the polymorphic form in the finished product was investigated during the stability studies and no conversion of the polymorphic form is observed.

In addition, one batch of the finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is photo-stable as it did not show signs of degradation after exposure to light without the protection of the primary packaging material.

One batch of the finished product was exposed to the forced degradation conditions of acid, base, oxidative, light plus moisture and heat plus moisture. Results confirmed the suitability of the assay and purity methods to separate and quantify relugolix and potential degradation products and to confirm that the methods are stability indicating.

An in-use, open-dish, stability study under ambient conditions was performed on one batch of the finished product. The samples were tested before and after 28 days. No difference in any of the tested quality attributes is observable. Based on these results, no in-use shelf life for the HDPE containers after opening is considered acceptable.

Based on available stability data, the proposed shelf-life of 36 months, without any special storage conditions, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

The Fixed Dose Combination product of relugolix, 17β-oestradiol (E2) and norethisterone (NETA), called Ryeqo, was submitted for evaluation by the same Applicant in the MAA procedure EMEA/H/C/005267/0000 and has been approved. As no new non-clinical studies were supplied, the non-clinical assessment of relugolix from the previous procedure is displayed below but it should be

noted that for the current indication a three-fold higher human clinical dose (120 vs 40 mg QD) is used and where needed the text has been adapted.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro – GnRH receptor binding

Relugolix showed a high affinity for human and for the monkey GnRH receptor with IC50 value of 0.12 nmol/L and 0.15 nmol/L, respectively. The binding affinity of relugolix for rat GnRH receptor was much lower, with IC_{50} values of 2,900 nmol/L.

In the presence of 40% FBS (fetal bovine serum), binding affinity of relugolix for human GnRH receptor was approximately 3-fold lower than that in the absence of FBS with IC50 value of 0.33 nmol/L. In contrast, GnRH, cetrorelix- a peptide GnRH antagonist - and TAP-144 – a peptide GnRH agonist - showed approximately the same affinities for GnRH receptors in the presence and absence of 40% FBS. But in either case, this affinity was lower than that of relugolix for human and monkey GnRH receptor in the presence of 40% FBS.

These results suggest that binding affinity of relugolix for human and monkey GnRH receptors is highly species-specific and is ~3-fold lower in the presence of serum, which is related to relugolix protein binding.

In vitro – functional effects on GnRH

The antagonistic effect of relugolix and cetrorelix was examined on CHO cells expressing human GnRH receptors. These compounds inhibited GnRH-induced 3H-arachidonic acid release in a dose-dependent manner. IC50 values were 0.32 and 0.67 nmol/L, and IC90 values were 2.6 and 4.6 nmol/L for TAK-385 and cetrorelix respectively. Relugolix being approximately 2-fold more potent than cetrorelix.

The antagonistic effect of these compounds in the presence of 40% human plasma was also determined. IC50 values were 1.6 and 4.5 nmol/L, and IC90 values were 18 and 75 nmol/L for relugolix and cetrorelix and respectively. IC50 values and IC90 values for relugolix were approximately 3-fold and 4-fold more potent with regard to antagonistic activity compared to cetrorelix in the presence of human serum. These data suggest that relugolix might show a potent GnRH antagonistic effect in human.

Relugolix showed an inhibitory effect on GnRH - induced arachidonic acid release from CHO cells expressing monkey GnRH receptors in a dose-dependent manner. Relugolix had a potent GnRH antagonistic effect even in the presence of 40% monkey plasma. These data suggest that relugolix would show a potent antagonistic activity in monkey models *in vivo*, providing further support for the *in vivo* study in monkey.

In vivo – human GnRH knock-in mice

As relugolix has only low affinity for the mouse GnRH receptor, a human GnRHR knock-in mice was generated, in which mouse GnRHR was replaced by human GnRHR, to evaluate the effect of relugolix on a hypothalamic-pituitary-gonadal axis. To clarify whether relugolix works as an antagonist for human GnRHR *in vivo*, the effect of chronic oral administration of relugolix on oestrous cycle, ovary and uterus weights, GnRHR mRNA expression in the pituitary, and bone density in female human GnRHR knock-in (KI) mice was examined. Also, the effect of oral administration of relugolix on the

weight of reproductive organs and pituitary human GnRH receptor mRNA expression in male human GnRH receptor KI mice was evaluated.

Relugolix (in 0.5% methylcellulose (MC) containing 6 mg/mL citric acid) was administered by oral gavage for 4 weeks at 30, 100, or 200 mg/kg BID in females and at 3, 10, or 30 mg/kg b.i.d. in males. For both females and males, two control groups were included in each study to receive 0.5% MC vehicle alone: intact (non-ovariectomized/non castrated) animals and ovariectomized/castrated animals.

The intact female mice displayed normal oestrous cycles, whereas OVX mice showed di-oestrous stage throughout the study period. Oral administration of relugolix induced a constant di-oestrous phase at the minimum dose of 100 mg/kg, b.i.d. and significantly decreased the ovary and uterus weight suggesting that relugolix suppresses the secretion of LH and oestrogens. In addition, relugolix at 100 mg/kg, b.i.d. also induced down-regulation of the GnRHR mRNA expression in the pituitary indicating that a non-peptide GnRH antagonist (relugolix), as well as a peptide GnRH antagonist (Cetrorelix), is able to down-regulate the expression of pituitary GnRHR mRNA. There were no differences in cancellous and cortical bone density between intact, OVX and each treatment group. These results indicate that relugolix has suppressive effects on the hypothalamic-pituitary-gonadal axis in female human GnRHR knock-in mice and suggest that relugolix could work as an oral antagonist for human GnRHR *in vivo.*

Significant decreases in ventral prostate weight, seminal vesicle weight, and pituitary human GnRH mRNA expressions were observed in castrated male mice. Oral administration of relugolix at doses higher than or equal to 3 mg/kg significantly decreased the ventral prostates and seminal vesicles weight. Furthermore, the effect of relugolix at a dose of 10 mg/kg on the weight of ventral prostates and seminal vesicles was similar to that of castration. These data suggest that relugolix would strongly reduce serum testosterone levels in human GnRH receptor KI mice. Relugolix at doses higher than 10 mg/kg, significantly decreased the human GnRH receptor mRNA expression in pituitaries. This suggests that relugolix, which is a non-peptide GnRH receptor antagonist would work as a GnRH receptor down-regulator in KI mice pituitaries such as is observed for peptide GnRH receptor antagonist cetrorelix in male rats. Our data indicate that relugolix has a suppressive effect on the hypothalamus-pituitary-gonadal axis in male human GnRH receptor KI mice.

In female hGnRH KI mice relugolix act as an orally active GnRH antagonist and suppresses the hypothalamic-pituitary-gonadal axis, suggesting that relugolix could therefore potentially be efficacious for treatment of reproductive disorders such as endometriosis and uterine leiomyoma. In male hGnRH KI mice, relugolix suppressed the weight of ventral prostates and seminal vesicles, and pituitary human GnRH receptor mRNA in male human GnRH receptor KI mice, suggesting that relugolix could have the potential to be efficacious for treatment of androgen dependent disorders such as prostate cancer by suppressing a hypothalamus-pituitary-gonadal axis. It is remarkable that an efficacious dose in male hGnRH KI mice is approximately ten times lower than an efficacious dose in female hGnRH KI mice. One of the primary effects of antagonism of the GnRH receptor, decreases in LH and FSH was not addressed in these studies.

In vivo – castrated monkeys

Castrated monkeys (3 per dose group) were treated with relugolix at a single dose of 0.1, 0.3, 1.0 or 3.0 mg/kg. Plasma was collected pre-treatment (0h) and 1, 2, 4, 8, 24 and 48 hours post treatment. Testosterone levels were determined using mouse testicular cells that were incubated with the monkey plasma. The corresponding LH concentrations in the samples were calculated by logistic regression analysis. The LH levels seem quite variable as for instance for one out of the three monkeys in the 0.3 mg/kg dose group deviating from the other two and one animal in the 1 mg/kg group seems to deviate from the other two animals in the same group. However, this is regarded inherent to the assay. The

results show that relugolix at doses of 1 and 3 mg/kg suppressed plasma LH levels in castrated cynomolgus monkeys with maximum suppression that continued for 24 and 48 hours after administration, respectively. In contrast, relugolix at doses of 0.1 and 0.3 mg/kg did not show substantial suppression. Thus, this *in vivo* experiment indicates that relugolix is orally active and effective at dose of over 1 mg/kg in castrated cynomolgus monkeys.

2.5.2.2. Secondary pharmacodynamic studies

Effects of relugolix on 134 MDSPS assays in Enzyme and Radioligand Binding Assays were investigated. Relugolix in primary screen assays was found to inhibit [^{3}H]SR-49868 binding to tachykinin NK2 receptors with the activity of 55% at 10 µmol/L. Relugolix had high affinity for the human GnRH receptor with an IC_{50} value of 0.12 nmol/L, which indicates that the affinity of relugolix to human GnRH receptor was ~83,000 times higher than that to tachykinin NK2 receptors. The results show that relugolix has a high specificity for the human GnRH receptor. As the steady state C_{max} for relugolix in humans is 79.1 ng/mL, binding to the tachykinin NK2 receptor is not anticipated to occur in the clinic.

2.5.2.3. Safety pharmacology programme

Relugolix inhibited hERG potassium channel current by 3.4%, 20.5% and 78.5% at 0.3, 3 and 30 µg/mL respectively and with an IC50 of 9.7 µg/mL (15.5 µM). This IC50 is approximately 123-fold higher than the mean total steady state Cmax of 79.1 ng/mL, reached upon administration of 120 mg relugolix once daily. This is regarded a sufficient large safety margin for hERG inhibition to occur in the clinic, especially since the unbound relugolix Cmax is even ~3-fold lower, resulting in an even higher safety margin.

Relugolix was administered to telemetered male cynomolgus monkeys (n = 4) at single doses of 0, 30, 100, or 300 mg/kg by oral gavage at 7-day intervals in a crossover manner. The no observed effect level (NOEL) for blood pressure and heart rate (changes in the systolic, diastolic, or mean blood pressures; heart rate; PR interval; or QRS duration) was 300 mg/kg and estimated to correlate with a mean Cmax of 10,400 ng/mL being approximately ~131-fold higher than the human Cmax (79.1 ng/mL at a dose of 120 mg/kg/day). As QT and QTc prolongation was observed in monkeys upon 100 mg/kg and 300 mg/kg single dose, the NOEL for QT/QTc interval prolongation was 30 mg/kg and estimated to correlate with a mean Cmax of 1740 ng/mL and approximately 22-fold higher than the human Cmax (79.1 ng/mL at a dose of 120 mg/kg/day). Relugolix did not prolong the QTcF interval in the clinical thorough QTc study at single doses up to 360 mg (mean Cmax 253 ng/mL). Therefore, the no effect level for QT prolongation in humans is at least ~3.2 fold higher than the mean total relugolix Cmax at steady state in humans associated with the anticipated clinical dose of 120 mg once daily (79.1 ng/mL).

Relugolix was administered to male Sprague Dawley rats (n = 6/group) as a single oral dose via gavage (dose volume = 10 mL/kg) at dose levels of 0 (0.5% MC), 200, 600, or 2000 mg/kg. No acute CNS effects in male rats at doses ≤ 2000 mg/kg at any time point up to 24 hours post-dose estimated to correspond with a Cmax of 7544 ng/mL which is approximately 95-fold higher than the human Cmax (79.1 ng/mL at a dose of 120 mg/kg/day).

Relugolix was administered to male Sprague Dawley rats (n = 8/group) as a single oral dose via gavage (dose volume = 10 mL/kg) at dose levels of 0 (0.5% MC), 200, 600, or 2000 mg/kg and respiratory function was evaluated using a whole-body plethysmography system measuring respiratory

rate, tidal volume, minute volume, enhanced pause [Penh] before and at 1, 2, 4, 8, and 22 hours post-dose. Relugolix had no acute effects on the respiratory system in male rats at doses up to 2000 mg/kg for 22 hours post-dose estimated to correspond with a Cmax = 7544 ng/mL which is approximately 95-fold higher than the human Cmax (79.1 ng/mL at a dose of 120 mg/kg/day).

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed for relugolix.

2.5.3. Pharmacokinetics

Absorption after single dose was investigated in rats and monkeys and after repeated dose in mice, rats, rabbits and monkeys. Tissue distribution was investigated in rats. Placental transfer and distribution to milk were investigated in rats. Metabolism was investigated in vitro and in vivo in rats and monkeys. Excretion was investigated in mass balance studies in rats (intact and bile-duct cannulated rats) and monkeys.

Methods of analysis

Validated methods were used for the toxicokinetic analyses in plasma of mice, rats, rabbits and monkeys. The validation was adequate regarding calibration, accuracy, precision, LLOQ, dilution integrity, matrix effect and stability. In the toxicokinetic studies, bioanalytical reports were provided. The calibration and QC samples met the criteria of the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev 1 Corr 2). The methods used in the pharmacokinetic analyses were fit for purpose.

Absorption

Relugolix has moderate intrinsic permeability in Caco-2 cells. Relugolix is a substrate for P-gp but it is not a substrate for BCRP.

After oral single dose administration, relugolix was absorbed rapidly in rats and monkeys (Tmax 1-3 h). The exposure increased more than dose-proportionally in rats up to 100 mg/kg and monkeys up to 20 mg/kg (maximally approximately 2-fold more than the increase in dose, based on AUC). In rats, relugolix was absorbed mainly from the small intestine, especially from the duodenum. Relugolix was absorbed via the portal route and not via the lymphatic route in rats. In monkeys, plasma exposure was considerably higher in fasted conditions than in fed conditions (Cmax 5-fold higher and AUC 21-fold higher). Volume of distribution was 16 – 39 L/kg in rats and 20 L/kg in monkeys, which implies a wide distribution beyond the total body water. Absolute oral bioavailability was low in rats, but some variation was visible (ranging 9 – 25% based on relugolix in the single dose pharmacokinetic studies). In the excretion study in bile-duct cannulated rats, 37% of total radioactivity was excreted in bile and 2.6% excreted in urine, indicating a bioavailability of approximately 40%. In monkeys, absolute oral bioavailability compared to IV administration was 6.9% at 1 mg/kg under fasted conditions. Estimated oral bioavailability in humans is 12%. Elimination half-life was 2-6 h in rats and 5-7 h in monkeys and 60 h in humans. Clearance was 4.5 – 9.3 L/h/kg in rats and 2.8 L/h/kg in monkeys, which is comparable to, or slightly exceeding hepatic blood flow. Only males were used in the single dose pharmacokinetic studies. In the toxicokinetic studies, both sexes were investigated, and no clear gender difference was observed. Therefore, no relevant gender differences are expected in other aspects of the pharmacokinetics.

After multiple dose administration, relugolix concentrations in plasma increased more than dose-proportionally at lower doses (mouse 10-100 mg/kg/day, rat 10-100 mg/kg/day, monkey 1.5-15 mg/kg/day) and approximately dose-proportionally or less than dose proportionally (mouse) at higher doses. No clear gender effect was observed in mice, rats and monkeys. No significant accumulation was observed in monkeys and in mice, except in monkeys at the lowest dose of 1.5-5 mg/kg/day and in mice at the highest dose of 2000 mg/kg/day. In rats, accumulation was observed at all doses. In general, accumulation in rats was approximately 4-fold, except at the lowest dose (10 mg/kg/day, more than 10-fold).

Distribution

Plasma protein binding of relugolix was moderate in mice (80-83%), rats (74-76%), monkeys (57-59%) and humans (68-71%) in the concentration range 0.05 – 5 µg/mL. Binding to human serum albumin and α1-acid glycoprotein combined was lower (38-44%) than binding in human plasma, showing that other proteins may also be involved. *In vitro*, relugolix had no relevant effect on plasma binding of highly bound compounds warfarin, ibuprofen, digoxin and propranolol.

Blood/plasma ratio in rats was 1.5 and 1.3 in males and females respectively at 4 h after dosing. *In vitro*, relugolix-associated radioactivity distributed into blood cells of rats, monkeys and humans for 45-49%, 57-59% and 46-41% respectively, which is a considerable proportion.

Following single dose oral administration to rats, relugolix-associated radioactivity was widely distributed with the highest concentrations in pituitary (up to 133x and 58x plasma concentration in males and females respectively) thyroid gland (71x and 54x), liver (294x and 170x), adrenals (55x and 55x), kidney (54x and 63x) and GI tract. Maximum concentrations were found at 4-8 h after dosing, except for the GI tract, where maximum concentrations were found at 1 h after dosing. At 168 h after dosing, concentrations were below the limit of quantitation or at trace levels in most tissues. Relugolix-associated radioactivity distributed similarly to pigmented and non-pigmented skin. Relugolix distributed to the eye, where it could still be found at 12 weeks after dosing. The potential for phototoxicity has been studied and no evidence of phototoxicity was found in mice. Low concentrations were found in the brain up to 24 h after dosing. Concentrations in brain were lower than or similar to concentrations in plasma.

Relugolix-associated radioactivity passed the placenta and was found in foetal plasma and tissue in rats. Cmax in foetal plasma was approximately 10% of maternal Cmax. Relugolix-associated radioactivity distributed into the milk of lactating rats. Concentrations in milk were high compared to plasma (approximately 10-fold at 2 h after dosing, the time of the maximum concentration). At 48 h after dosing, still measurable concentrations could be found. The data show that relugolix and relugolix-associated material (e.g. radioactive relugolix metabolites) has the potential to accumulate in milk.

Metabolism

In vitro, the major compound found in microsomes of mice, rats, dogs, monkeys and humans was the parent compound. In the presence of NADPH, the main human metabolites were Metabolite-A and Metabolite-B. Metabolite A was also formed in monkeys, and to a minor extent also in dogs, mice and rats. Metabolite-B was also formed in mice and rats and only to a very low extent in monkeys and dogs. Other metabolites, T-1400567, T-1525140, UK-A and UK-C, were formed to a low extent. An unidentified metabolite UK-E is also mentioned. No quantitative data are given regarding the formation of this metabolite. However, since it was not formed in a previous study and it was also not mentioned in the *in vivo* studies, it is probably not formed in relevant quantities. In the absence of NADPH, T-1525140 was formed in all species and the other metabolites only to a very low extent. In dog microsomes, relugolix underwent less metabolic turnover than in microsomes from the other species.

Metabolite A was formed through O-demethylation by CYP3A4. Metabolite B was formed through hydroxylation by CYP2C8 and, to a low extent, by CYP2C19. Metabolite C was formed through N-demethoxylation, but not by CYP enzymes. Metabolite-C was found in large amounts only in faeces and it was formed in incubations with human faecal homogenates, but not in autoclaved faecal samples and is therefore most likely formed by gut microflora.

In vivo metabolism was investigated in rats and monkeys and humans. Unchanged relugolix was the most abundant component in the plasma. At the time of the maximal radioactivity concentration (2 h in rats and 4 h in monkeys), mainly unchanged relugolix was present at 99% of radioactivity in rats and at 86% in monkeys. In humans at 72 h, unchanged relugolix in plasma ranged from 42 to 68% of total radioactivity. Metabolite-A was found up to 8.7% in plasma of monkeys, whereas it was not found in plasma of rats. Metabolite-B was not found in plasma of rats or monkeys, but it was found in bile of rats. Metabolite-C was found up to 1.9% in plasma of rats and not in plasma of monkeys. Remaining radioactivity consisted of minor, unidentified components. Even though at later time points (at 6 h in rats and 24 h in monkeys) "other components" comprised up to 40% of radioactivity in plasma in rats and up to 77% in monkeys, in absolute sense this concerns only minor amounts. In humans, all metabolites in plasma, which could amount up to 58%, were separately present at < 5% of total radioactivity. There are therefore no major human metabolites that need to be covered in the non-clinical species. Most of relugolix-related material was excreted as metabolites with unchanged relugolix accounting for ≤ 8.0% in excreta of rats and monkeys. In bile of rats, Metabolite-B was the major compound. Metabolite-C was the major component in faeces of rats (59% of dose), monkeys (45% of dose) and also humans (40% of dose). Since Metabolite-C was not present in plasma or only at very low levels, and it was also not formed in incubations with intestinal microsomes, it was probably formed by gut microflora. This was confirmed by inhibition of Metabolite-C formation by autoclaving human faecal homogenates or by treatment of these homogenates with antibiotics.

Excretion

Recovery in the excretion studies following a single oral dose to rats and monkeys was 93-100% of the dose. The major part of relugolix-related radioactivity was excreted via the faeces (92-96% in intact rats and orally-dosed monkeys). In rats, only a minor part was excreted via the urine (1.4-2.6%). In monkeys, the excretion via urine was more variable (4.9-22% after oral administration). In bile-duct cannulated rats, 37% of the dose was excreted via the bile 24 h after administration of [^{14}C]-relugolix. In monkeys, a large part appears to be excreted via the bile (69% of dose was excreted via faeces after IV administration). Yet, a considerable part was excreted via the urine as well (24% after IV administration). In humans, the same pattern was observed as in rats (83% excreted in faeces and 4.4% in urine).

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

In rats, a single IV dose of 90 mg/kg relugolix was lethal for all animals. The maximum tolerated single oral dose of relugolix in mice, rats and monkeys is at least 2000 mg/kg.

2.5.4.2. Repeat dose toxicity

Although relugolix demonstrates a very low affinity for rodent GnRH receptors, mice and rats are appropriate models to evaluate potential chemical-based or off-target toxicologic effects of relugolix. Oral treatment of mice during 4 weeks with 2000 mg/kg/day resulted in necrosis of the renal tubules

and increased incidence of tubular basophilia in both sexes. After 13 weeks, at 2000 mg/kg/day in mice, similar histopathology findings were found in kidneys, spleen, colon, cecum, and femur and sternum bone marrow and corresponding effects on kidney and spleen weights, as well as effects on red blood cell (RBC) parameters. In the spleen, minimal to mild increased extramedullary haematopoiesis was observed. The NOAEL based on these effects was 600 mg/kg/day which is 141-fold higher than the intended human dose, based on AUC.

In rats after an oral treatment of 2 weeks, foamy cell infiltration in the testis was observed in 2 males at 100 mg/kg/day and in all males at 300 mg/kg, findings associated with phospholipidosis (PLD). After 4 week treatment in rats, at 2000 mg/kg relugolix some animals died, the liver enzymes ALT and AST increased, the urine was cloudy, and in various tissues cytoplasmic vacuolization, foamy cell infiltration, increased tingible body macrophages and necrosis due to PLD were shown. At 300 mg/kg, PLD-related histopathology was shown already, like foamy cell infiltration in lung and testis, vacuolization of tubular epithelial cells in kidney, and increased tingible body macrophages in the mesenteric lymph nodes. After 13 week treatment, in rats at 1000 mg/kg one male died. Urine was cloudy and necrosis in several tissues due to PLD was seen. At ≥300 mg/kg (females) and ≥100 mg/kg (males) signs of PLD were observed (cytoplasmic vacuolization and foamy cell infiltration in various tissues, increased tingible body macrophages in lymphoid tissues and bone marrow). After 26 week treatment at 300 mg/kg, cloudy urine was observed sporadically in a few male and female rats. At ≥ 100 mg/kg males showed signs of PLD in testis. The prolongation of the dosing period of relugolix from 4 or 13 weeks to 26 weeks did not intensify PLD in rats to at least the dosage level of 300 mg/kg. Further, necrosis was not observed in these organs or tissues at this dose level.

Based on the PLD findings of the 26 week study in rats, the NOAEL is 30 mg/kg for males and 100 mg/kg for females, which is 3 times, respectively 11 times the intended human exposure. However, organ toxicity, adverse clinical signs, and mortality were not observed at the highest dose of 300 mg/kg. The NOAEL for organ toxicity was therefore considered 300 mg/kg in both sexes and around 55 times higher than the intended human exposure. In conclusion, rodent studies do not indicate off-target toxic effects at intended human exposures.

The cynomolgus monkey was selected as the non-rodent species because of the high sequence homology with the human GnRH receptor (97.5% compared to 92.1% in dog) and the similar affinity and potency at the GnRH receptor relative to dogs. When relugolix was administered by oral gavage to cynomolgus monkeys for 2 weeks, dark discoloration of the liver which corresponded histologically to bile plugs, pigmentation of the hepatocytes and sinusoidal cells, and single cell necrosis of the hepatocytes were noted at 100 mg/kg. Histopathology findings in the gastrointestinal tract (foamy cell infiltration in the duodenum and cecum, vacuolization of the parietal cells in the stomach) were noted in males at ≥ 40 mg/kg and females at 100 mg/kg. A supplementary 2-week study in cynomolgus monkeys was followed with three doses up to 15 mg/kg/day, which is 7.7 times higher than the intended human exposure, to investigate dosage levels not associated with PLD-related observations. However, in the first study no PLD-related observations were made at 20 mg/kg/day, so this second study was unnecessary and indeed, no relugolix-related effects were seen.

In a 4-week oral gavage study in monkeys, increases in ALT/AST and histopathology findings in the liver were noted at 100 mg/kg/day. Findings of PLD (foamy cell infiltration in the submandibular and mesenteric lymph nodes and increased tingible body macrophages in several tissues) were observed at ≥ 10 mg/kg/day. In a 39-week study, relugolix (1.5, 5, 15, or 50 mg/kg/day) was administered by oral gavage to cynomolgus monkeys followed by a 13-week recovery period. The major toxicologic finding was observed in the liver (primarily changes in clinical chemistry) at 50 mg/kg. At the end of the recovery period, there was an overall decrease in the incidence and/or severity of liver findings, indicating ongoing recovery, and full reversibility was observed for the changes of transaminase levels. Reversible changes in female sex organ weight were observed at 50 mg/kg; this finding was attributed

to the mechanism of action (GnRH antagonism). PLD was observed in various organs, and the number of affected organs increased with dose, but no marked adverse toxicities were associated with PLD. Histopathology findings indicative of PLD (foam cell infiltration in the submandibular lymph node, increased tingible body macrophages, and vacuolization in parietal cells of the stomach) were observed in males and/or females at ≥ 5 mg/kg. The PLD-related findings showed evidence of recovery. The NOAEL based on PLD is 1.5 mg/kg/day in both sexes, which is 0.4-fold higher than the intended human exposure. The NOAEL for organ toxicity was 15 mg/kg in both sexes based on liver toxicity, which is 9.3-fold higher than the human intended dose. In conclusion, no serious toxic effects are shown in monkeys at clinical exposures of relugolix.

In a phospholipidosis biomarker study in rats, 0, 30 and 1000 mg/kg/day was orally dosed for 28 days. The study evaluated the sensitivity of di-22:6-BMP as a biomarker for PLD following relugolix exposure. The biomarker di-22:6-BMP was measured in urine, serum, lungs, and testes. At 1000 mg/kg, light microscopy (mild foamy cell infiltrates in the lungs/lymph nodes), TEM (prominent multilamellar cytoplasmic bodies in lymphocytes), and di-22:6-BMP biomarker analysis (2- to 3-fold increase in urine, lungs, and testes) demonstrated relugolix-related changes indicative of PLD. At 30 mg/kg, no such effects were seen. Thus possibly, urinary di-22:6-BMP can serve as a potential biomarker for detection of PLD in rats exposed to relugolix. A clinical study with up to 120 mg relugolix QD for up to at least 24-weeks did not show meaningful alterations in di-22:6-BMP. This indicates that PLD is not likely to occur in patients at the intended dose.

2.5.4.3. Genotoxicity

Relugolix was negative in a bacterial reverse mutation (Ames) assay, an *in vitro* chromosomal aberration assay, and in a rat *in vivo* micronucleus assay, indicating that relugolix does not present a genotoxic risk.

2.5.4.4. Carcinogenicity

There was no evidence of treatment-related effects on the incidence of any tumours or in the number of tumour bearing animals in mice administered relugolix up to 100 mg/kg and in rats administered relugolix up to 600 mg/kg for 2 years. Exposure margins are both more than 50 times the intended human exposure based on AUC.

2.5.4.5. Reproductive and developmental toxicity

Relugolix was administered to male and female rats at doses up to 1000 mg/kg/day in a fertility and early embryonic development study. Relugolix had no adverse effects on the oestrous cycle in female rats up to 1000 mg/kg, and no adverse effects were noted on reproduction or early embryonic development. Only minor effects on food consumption and body weight were noted at the highest dose. However, given the low binding affinity of relugolix for rat GnRH receptors, the results provide an assessment of off-target effects of relugolix only.

Based on literature (Nakata et al. 2014), the Applicant showed that in female human GnRH receptor knock-in mice, the suppressive effects of relugolix on the hypothalamic-pituitary-gonadal axis at doses of ≥ 100 mg/kg twice daily, induced a constant di-oestrous phase, and caused decreases in both ovarian and uterine weights. Withdrawal of relugolix after 28 days resulted in recovery of female reproductive function from a completely suppressed state in approximately 5 days, followed by continuous oestrous phases for several days. Subsequently, the oestrous cycles and the weight of hormone-dependent organs almost recovered to normal within 14 days after drug withdrawal. In

monkeys (see repeat-dose study TAK-385/00144), decreases in the frequency in menses were observed at 50 mg/kg for up to 39 weeks where all females at 50 mg/kg did not have menses after Day 13, probably related to the pharmacologic effects of relugolix. Additionally, menses in female monkeys demonstrated a recovery tendency within 13 weeks after last treatment. In male human GnRH receptor knock-in mice, relugolix decreased ventral prostate and seminal vesicle weights in a dose-dependent manner from 3 to 10 mg/kg BID. The suppressive effects on ventral prostate weight and serum testosterone concentrations were reversible as there was a return to pre-dose levels within 14 days following cessation of treatment; however, testis weight (~30 % to 40 % decrease) did not fully recover after 28 days. This lack of recovery may be due to incomplete recovery in cell number of the spermatogenic epithelium, which occupies a large component of testicular weight, during this period (Nakata et al. 2014). In conclusion, relugolix has inhibitory effects on the male (at low doses) and female (at high doses) reproductive system, based on its pharmacodynamic action, which is only partly reversible.

As the current indication of prostate cancer is applicable to males only, the embryofoetal development studies are not relevant. However, a summary of the assessment is provided: In an embryofoetal development study in rats, relugolix was administered to pregnant animals on GDs 6 to 17 at doses up to 1000 mg/kg/day. Treatment-related lower body weight, suppression of body weight gain, and decreased food consumption were observed at various intervals of the administration period at 1000 mg/kg, giving a NOAEL for maternal toxicity of 200 mg/kg. There were no relugolix-related changes in pregnancy status or foetal endpoints. The NOAEL for embryofoetal developmental toxicity was 1000 mg/kg (exposure is 170 times the intended human dose) in this pharmaceutically unresponsive model. In an embryofoetal development dose range-finding study in the more relevant species rabbits, relugolix up to 1000 mg/kg was administered on GDs 6 to 18. Relugolix appeared very toxic for rabbits and on GD 12 to 15, all females at 1000 mg/kg died, and from 40 mg/kg on, there were no implants. Some females at 8 mg/kg lost entire litters (total resorptions) during the early phase of the dosing period. These changes are considered related to the pharmacological effects of relugolix. The frequency of skeletal variations at 8 mg/kg was high. In the pivotal study, rabbits were dosed much lower with 0.3 to 9 mg/kg. At 9 mg/kg, total litter loss was observed in 7 of 20 animals and high post-implantation loss rate, a significant decrease in live foetuses, and low foetal viability rate were noted. There were no abnormalities or variations in external, visceral, or skeletal observations. The NOAEL for embryofoetal developmental toxicity was 3 mg/kg, which is far below the relugolix exposure (AUC) at the proposed clinical dose.
As the current indication of prostate cancer is applicable to males only, the pre- and postnatal development studies are not relevant. However, a summary of the assessment is provided: In a prenatal and postnatal development study in the pharmacologically unresponsive rat model, relugolix had no effect on maternal function in F0 dams, development in F1 pups/animals, reproductive function in F1 animals, and early embryonic development at exposures up to 1000 mg/kg.

2.5.4.6. Other toxicity studies

The phototoxic potential of relugolix was evaluated in an in vitro phototoxicity neutral red uptake (NRU) assay using BALB/3T3 clone A31 cells, and relugolix elicited a phototoxic response. However, according to the ICH Guidance S10 on Photosafety Evaluation of Pharmaceuticals, a positive result in this test should not be regarded as indicative of a likely clinical phototoxic risk, but rather a flag for follow-up assessment. Hereafter, the Applicant performed an in vivo phototoxicity study (GLP) in hairless mice, and skin reactions indicative of phototoxicity were not observed in any of the mice at doses up to 2000 mg/kg followed by exposure of UV-radiation. Therefore, relugolix is considered not phototoxic.

2.5.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) for relugolix has been assessed during the MAA of Ryeqo, as part of procedure EMEA/H/C/005267/0000. The applicant submitted an updated ERA for relugolix including data of a zebrafish extended one generation reproduction test (ZEOGRT) study.

Summary of main study results

Substance (INN/Invented Name): relugolix			
CAS-number (if available): 737789-87-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} -0.57, 0.85 and 2.7 at pH 5, 7 and 9	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	-0.57 at pH 5.1-5.2 0.85 at pH 7.1 2.7 at pH 9.1	not B
Persistence	ready biodegradability	not ready	
	DegT50 parent	$DT_{50, water}$ = 3.2/11 d (l/l) $DT_{50, sediment}$ = 72/176 d (l/l) $DT_{50, system}$ = 70/148 d (l/l)	l=lake. DT_{50} values corrected to 12°C. Conclusion: P
	DegT50 metabolites	TP1: $DT_{50, system}$ = 17 d (l) TP5: $DT_{50, system}$ = 129d (l)	Conclusion: not P Conclusion: P
Toxicity	EC10 algae NOEC crustacea NOEC fish	2.1 mg/L ≥2.5 mg/L <0.32 µg/L* EC10 0.103	T
	CMR	not investigated	potentially T
PBT-statement:	relugolix is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water\ (refined)}$	2.66	µg/L	> 0.01 threshold (Y)

Other concerns (e.g. chemical class)	potential reproductive effects on vertebrates and/or lower animals. Action limit does not apply.				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ 353, 233 L/kg $K_{oc\ soil}$ 8781, 28346, 289871 L/kg			
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 1.5/5.3 d (l/l) $DT_{50,\ sediment}$ = 34/83 d (l/l) $DT_{50,\ system}$ = 33/70 d (l/l) % shifting to sediment = 9% and 26%			l=lake; DT_{50} values at 20°C; Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*R. subcapitata*	OECD 201	EC10	2.1	mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥2.5	mg/L	reproduction, growth, mortality
Fish, Zebrafish extended one generation reproduction test (ZEOGRT) / *Danio rerio*	-	NOEC EC10	<0.32* 0.103**	µg/L	F2, hatching
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC10	≥1000 >1000	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	1253	mg / kg_{dw}	development; normalised to 10% o.c.

* 18% effect was observed at the lowest test concentration of 0.32 µg/L (mean measured value), a NOEC cannot be derived.
** The EC10 is a factor of 3 below the lowest test concentration.

2.5.6. Discussion on non-clinical aspects

Pharmacology

In vitro, relugolix binds to the GnRH receptor with IC_{50} value of 0.12 nmol/L and in the presence of serum with IC_{50} value of 0.33 nmol/L (approximately 3-fold lower affinity). The antagonistic effects of

relugolix and cetrorelix on CHO cells expressing human GnRH receptors was examined by measuring the GnRH-induced 3H-arachidonic acid release in a dose-dependent manner. The IC_{50} value was 0.32 nmol/L (1.6 nmol/L in the presence of serum) and IC_{90} value was 2.6 nmol/L (18 nmol/L in the presence of serum) for relugolix.

In female hGnRH KI mice relugolix act as an orally active GnRH antagonist and suppresses the hypothalamic-pituitary-gonadal axis, suggesting that relugolix could therefore potentially be efficacious for treatment of reproductive disorders such as endometriosis and uterine leiomyoma. In male hGnRH KI mice, relugolix suppressed the weight of ventral prostates and seminal vesicles, and pituitary human GnRH receptor mRNA in male human GnRH receptor KI mice, suggesting that relugolix could have the potential to be efficacious for treatment of androgen dependent disorders such as prostate cancer by suppressing a hypothalamus-pituitary-gonadal axis. It is remarkable that an efficacious dose in male hGnRH knock-in mice is approximately ten times lower than an efficacious dose in female hGnRH knock-in mice. Unexpectedly, two of the primary effects of antagonism of the GnRH receptor, i.e. decreases in LH and FSH, were not addressed in these studies.

In addition, orally administered relugolix at doses of 1 and 3 mg/kg suppressed plasma LH levels in castrated cynomolgus monkeys with maximum suppression that continued for 24 and 48 hours after administration, respectively. In contrast, relugolix at doses of 0.1 and 0.3 mg/kg did not show substantial suppression. Thus, this *in vivo* experiment indicates that relugolix is orally active and effective at a dose of ≥1 mg/kg in castrated cynomolgus monkeys.

No secondary pharmacology or safety pharmacology effects are noted *in vitro* or *in vivo* in animals that would indicate for risks upon clinical use of relugolix.

Pharmacokinetics

The non-clinical pharmacokinetics have been studied adequately.

Toxicology

Relugolix is not toxic in rodents like mice and rats up to very high doses when administered orally, and the toxic effects shown at those very high doses are also off-target toxic effects, because relugolix has a very low affinity for rodent GnRH receptors. Relugolix in the cynomolgus monkey has a high affinity for the human GnRH receptor, and also shows effects at lower doses than in rodents, like on the liver, still with a large margin of exposure compared to humans. The only effect seen in monkeys at relatively low doses is phospholipidosis (PLD) in various organs with a low safety margin. But PLD is not considered a serious toxic effect, and also by use of a PLD-biomarker in humans with the normally intended dose of relugolix, no signs of PLD were shown.

The Applicant clarified that the current product for the treatment of advanced prostate cancer is being developed under the ICH S9 guideline and that several studies have been conducted under the ICH M3 guideline due to the development of a product for the treatment of uterine fibroids and endometriosis in women of childbearing age. In addition, reversibility data were provided supporting the reversibility of effects as observed in repeated toxicity studies of the cynomolgus monkey, which is the most sensitive species in contrast to rats and mice, for which relugolix had a weak affinity for the GnRH receptor. In rats and mice, toxicities are observed but at fairly high exposure levels compared to human exposure.

No treatment-related effects on fertility, embryo-foetal development and pre-post-natal development were reported in rats at doses up to 1000 mg/kg/day. As the rat is not a pharmacologically relevant species, these results are interpreted as an absence of off-target adverse effects on the parameters investigated in these studies. Relugolix may have adverse effects on male fertility due to its activity at GnRH receptors. In a published study in human male GnRH receptor knock-in mice, pharmacology-

related decreases in ventral prostate/testicular weight and testosterone concentrations were observed at ≥3 mg/kg/day. These effects were reversible, with the exception of the reduction in testicular weight, probably due to incomplete recovery of spermatogenic epithelial cell numbers. SmPC 5.3 should be revised to remove the lack of a treatment-related effect on testicular weight in the 39-week monkey study, since histopathological assessment organs showed that most male animals were sexually immature at the end of treatment. In the embryo-foetal developmental toxicity study in rabbits, spontaneous abortions and embryonic lethality were reported in the absence of maternal toxicity at 9 mg/kg/day. The Applicant supplied as requested further justification of the contraceptive measure proposed in SPC 4.6 for treated male partners of women of child-bearing potential. This justification is based on a risk assessment estimating the theoretical systemic exposure in a female partner from seminal transfer of relugolix, which is conservative, and the possible risk of foetal harm. In spite of a safety ratio of 162 between exposure of rabbits at the no-observed effect level in the EFD study and predicted Cmax in females partners of treated male patients exposed via seminal fluid, the Applicant considers that a risk cannot be fully excluded and still recommends a contraception measure for male patients. Indeed, it is argued that the predicted Cmax value in female partners of male patients is similar to the IC_{50} value determined at human GnRH receptor. Therefore, given the potential serious adverse effects due to this inhibition, a warning for contraception in males is warranted. The proposed 2-week period of contraception use following cessation of relugolix therapy is consistent with 5-times the elimination half-life.

Relugolix has found to have no genotoxic or carcinogenic potential, however, the relevance of the rat and mouse carcinogenicity studies for human carcinogenic risk assessment is limited given the very low binding affinity of relugolix for rat and mouse GnRH receptors. The studies are only directed at off target effects.

ERA

Relugolix is not PBT, nor vPvB. No risk was identified for micro-organisms in the sewage treatment plant (STP), for the groundwater compartment and for the sediment compartment. A risk assessment for the terrestrial compartment was not triggered. A risk to the aquatic compartment was identified. This has been reflected in the SmPC section 5.3 and 6.6 including the statement that any unused medicinal product or waste material should be disposed of in accordance with local requirements.

2.5.7. Conclusion on the non-clinical aspects

Relugolix is a nonpeptide GnRH receptor antagonist that competitively binds to GnRH receptors in the anterior pituitary gland preventing native GnRH from binding and signalling the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Non-clinical data based on conventional studies reveal no special hazard for humans beyond those discussed above. It is not known whether relugolix or its metabolites are present in semen. Based on findings in animals and mechanism of action, if a patient engages in sexual intercourse with a woman of childbearing potential, effective contraception during treatment and for 2 weeks after the last dose of Orgovyx must be used. There is a limited amount of data from the use of relugolix in pregnant women. Studies in animals have shown that exposure to relugolix in early pregnancy may increase the risk of early pregnancy loss. Based on the pharmacological effects, an adverse effect on pregnancy cannot be excluded. Results from nonclinical studies indicate that relugolix is excreted into the milk of lactating rats. No data are available regarding the presence of relugolix or its metabolites in human milk or its effect on the breast-fed infant. An effect on breast-feeding newborns/infants cannot be excluded. Based on findings in animals and mechanism of action, Orgovyx may impair fertility in males of reproductive potential (see SmPC section 4.6 and 5.3).

The non-clinical package submitted is considered adequate for the approval of Orgovyx.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2. Overview of Clinical Efficacy Studies in 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 (NCT03085095) (International) Primary Analysis (Cohort 1) Complete Final Analysis (Cohorts 1 and 2) Complete China Sub-analysis (Cohort 3) Ongoing	160/ North and South America, Europe, and the Asia Pacific Region	Multinational, randomized, open-label, parallel-group study	Males aged 18 years or older with androgen-sensitive advanced prostate cancer who are candidates for at least 1 year of continuous ADT	Efficacy and Safety	Relugolix 360 mg on Day 1 then 120 mg QD for 48 weeks Leuprolide 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) 3M depot injections for 48 weeks	Relugolix 719 (563 [a], 636 [b]) Leuprolide 359 (276 [a], 315 [b])	The study had 2 separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing benefit (Cohort 1, primary analysis): 1. FDA: To determine whether the sustained castration rate for relugolix is ≥ 90%. 2. EMA and PMDA: To establish the noninferiority of relugolix compared with leuprolide 3M depot injection as assessed by the cumulative probability of sustained testosterone suppression. For the final analysis (Cohort 2), the key secondary endpoint is Time to CRFS

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 (NCT02135445) (US, UK) Complete (21 Nov 2016)	23 sites/ US and UK	Two-arm, randomized, open-label, parallel-group study	Males 18 years or older with localized prostate cancer requiring neoadjuvant/ adjuvant ADT with EBRT	Efficacy, safety, and tolerability	Arm 1 Relugolix 320 mg on Day 1 then 120 mg QD for 24 weeks Arm 2 Two degarelix 120-mg SC depots on Day 1 then degarelix 80-mg SC depots Q4W starting on Week 5 Day 1	Arm 1 65 (63) Arm 2 38 (38)	Castration rate (< 50 ng/dL from Week 5 Day 1 through Week 25 Day 1)
C27002 (NCT02083185) (North America) Complete (05 May 2017)	23 sites/ US and Canada	Three-arm, randomized, open-label, parallel-group dose-finding study of relugolix, with a leuprolide observational cohort	Males 18 years or older with advanced hormone-sensitive prostate cancer requiring first-line ADT	Efficacy, safety, and tolerability	Arm 1 Relugolix 320 mg on Day 1 then 80 mg QD for 48 weeks[c] Arm 2 Relugolix 320 mg on Day 1 then 120 mg QD for 48 weeks[c] Arm 3 Leuprolide 22.5 mg depot Q12W for 48 weeks	Arm 1 56 (31) Arm 2 54 (26) Arm 3 24 (20)	Castration rate (< 50 ng/dL from Week 5 Day 1 through Week 25 Day 1)
TB-AK160108 (NCT02141659) (Japan) Complete (05 Dec 2017)	7 sites/ Japan	Two-part, open-label, dose range-finding study	Hormone treatment-naïve Japanese males 20 years or older with nonmetastatic prostate cancer	To evaluate the tolerability, safety, PK, and PD of relugolix alone in hormone treatment-naïve Japanese patients with non-metastatic prostate cancer	Part A Cohort 1 Relugolix 320 mg on Day 1 then 80 mg QD on Days 2 to 28 Part A Cohort 2 Relugolix 320 mg on Day 1 then 120 mg QD on Days 2 to 28 Part A Cohort 3 Relugolix 320 mg on Day 1 then 160 mg QD on Days 2 to 28 Part A Cohort 4 Relugolix 360 mg on Day 1 then 120 mg QD on Days 2 to 28 Part B 80 mg Relugolix 320 mg on Day 1 then 80 mg QD on Day 2 to Week 48[c] Part B 120 mg Relugolix 320 mg on Day 1 then 120 mg QD on Day 2 to Week 48[c]	Part A Total: 13 (12) Cohort 1: 3 (3) Cohort 2: 4 (3) Cohort 3: 3 (3) Cohort 4: 3 (3) Part B Total: 30 (26) 80 mg: 15 (13) 120 mg: 15 (13)	Part A: Safety: DLTs, AEs, clinical laboratory tests, vital signs, and 12-lead ECGs Part B: Safety: AEs, clinical laboratory tests, vital signs, and 12-lead ECGs

Abbreviations: 3-M = three-month; ADT = androgen deprivation therapy; AE = adverse event; CRFS = castration resistance-free survival; DLT = dose-limiting toxicity; EBRT = external beam radiation therapy; ECG = electrocardiogram; EMA = European Medicines Agency; PD = pharmacodynamic; PK = pharmacokinetic; PMDA = Pharmaceuticals and Medical Devices Agency; Q4W = every 4 weeks; Q12W = every 12 weeks; QD = once daily; SC = subcutaneous; UK = United Kingdom; US = United States.

[a] Number of patients in the primary analysis cohort (i.e., completed 48 weeks of treatment).

[b] Number of patients in the final analysis cohort (i.e., completed 48 weeks of treatment).

[c] Patients completing 48 weeks of relugolix treatment in study TB-AK160108 and study C27002 (Arm 1 and Arm 2) had the option to continue for up to 48 additional weeks (i.e., 96 weeks total) at their originally assigned relugolix dose level.

2.6.2. Clinical pharmacology

The clinical pharmacology program was designed to support both the prostate cancer program with relugolix as monotherapy as well as the women's health programs in uterine fibroids and endometriosis with relugolix combination therapy (relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg, see Ryeqo EPAR for more details). Therefore, both male and female participants were included in several clinical pharmacology studies. In addition, because dosing recommendations of relugolix for the prostate cancer indication is 120-mg once daily and for the women's health indications is 40 mg once daily (in combination with estradiol and norethindrone acetate), some clinical pharmacology data generated with relugolix 40 mg support the prostate cancer indication.

The clinical development program for Orgovyx included one (1) biopharmaceutics study and twelve (12) clinical pharmacology studies in healthy participants and patients with moderate and severe renal or mild and moderate hepatic impairment, and four (4) studies (one phase 1, two phase 2, and one phase 3) in men with prostate cancer, to support the marketing authorization application (MAA) of relugolix for the treatment of men with prostate cancer (**Table 3**).

Additionally, a population pharmacokinetic (PopPK) model and a population pharmacokinetic/ pharmacodynamic (PopPK/PD) model were developed using data from two clinical pharmacology (phase 1), two phase 2, and one phase 3 studies. The PopPK model was developed to characterize the pharmacokinetics of relugolix and to identify demographic or physiological covariates that explain interindividual variability on the exposure to relugolix. The PopPK/PD model was used to characterize the relationship between relugolix exposure and testosterone concentrations, identify covariates that impact pharmacodynamic parameters, and explain interindividual variability in testosterone concentrations.

Table 3. Data Contributing to the Clinical Pharmacology Assessment of Relugolix

Study (Region)	Short Title	Relugolix Dose(s) (mg)	Fasting Condition	Number of Male/Female Participants
Human ADME				
TAK-385_1009 (UK)	Human ADME and Absolute Bioavailability Study	80 mg oral SD 80 µg IV SD	Fasted	12/0
Biopharmaceutics study				
TAK-385_1010	Relative Bioavailability and Food-Effect Study of T4B, T4C, and T2 Relugolix Tablet Formulations	Group1: 120 mg oral SD	Fasted +Fed	Group 1: 27/0
Single and Multiple Rising-Dose Studies				
C27001 (UK)	Safety and Tolerability, Pharmacokinetic and Pharmacodynamic Study in Healthy Men (Prostate Cancer-Enabling Study)	Part 1 (SD): 80, 120, 180, 360, placebo Part 2 (once daily x 14 days): 80, 180, 360/40, 320/240/160/20, 320/160/20, placebo Part 3 (once daily x 28 days): 160, 320/160/40, placebo Part 4 (once daily x 28 days): 60, 80, placebo	Part 1: Fasted + Fed (Cohort 3) Parts 2, 3, 4: 30 min before meal	174/0 (126 relugolix, 48 placebo)
Intrinsic Factors/Special Populations				
MVT-601-1002 (US)	Mild and Moderate Hepatic Impairment Study	40 mg SD	Fasted	18/6
MVT-601-040 (US)	Moderate Renal Impairment Study	40 mg SD	Fasted	18/6
MVT-601-1003 (US)	Severe Renal Impairment Study	40 mg SD	Fasted	12/11

Study (Region)	Short Title	Relugolix Dose(s) (mg)	Fasting Condition	Number of Male/Female Participants
Drug Interactions: Victim Studies				
TAK-385/CPH-010 (Japan)	Erythromycin (P-gp and Moderate CYP3A Inhibitor) Drug Interaction Study	20 mg SD	30 min before meal	10/10
C27005 (US)	Fluconazole and Atorvastatin (Moderate and Weak CYP3A Inhibitor) Drug Interaction Study	40 mg SD	30 min before meal	20/20
MVT-601-043 (US)	Voriconazole (Strong CYP3A Inhibitor) Drug Interaction Study	40 mg SD 120 mg SD	Fasted	40 mg: 3/13 120 mg: 16/0
MVT-601-1004 (US)	Rifampin (Combined P-gp and Strong CYP3A Inducer) Drug Interaction Study	40 mg SD	Fasted	13/5
Drug Interactions: Perpetrator Studies				
MVT-601-044 (US)	Midazolam (CYP3A Substrate) Drug Interaction Study	40 mg QD for 14 days 120 mg QD for 14 days	1 hr before meal	40 mg: 3/9 120 mg: 12/0
MVT-601-045 (US)	Rosuvastatin (BCRP Substrate) Drug Interaction Study	40 mg QD for 14 days 120 mg QD for 14 days	1 hr before meal	40 mg: 4/8 120 mg: 12/0
Pharmacodynamic Studies				
TAK-385_106 (US)	Thorough QT/QTc Study	60 mg SD 360 mg SD	Fasted	60 mg: 36/34 360 mg 36/34
Pharmacokinetic and Pharmacodynamic Modeling				
MYOV-PMX-RELUGOLIX-1816 Report 01 MYOV-PMX-RELUGOLIX-1816 Report 01-Addendum01 - 04	Population Pharmacokinetic/Pharmacodynamic (PopPK/PD) Analyses	Various	Various	999/0

Abbreviations: ADME = Absorption, Distribution, Metabolism, Excretion; BCRP = Breast Cancer Resistance Protein; CYP3A = Cytochrome P450 3A; IV = intravenous; P-gp = P-glycoprotein.

Analytical methods

All bioanalytical methods for relugolix (and for testosterone) were validated as phase-appropriate in accordance with guideline documents and were shown to be accurate, precise, specific, sensitive, and reproducible. Interference testing was completed as necessary. Most methods have already been reflected in the Ryeqo procedure (EMEA/H/C/005267).

2.6.2.1. Pharmacokinetics

After oral administration, relugolix is rapidly absorbed, reaching maximum concentrations at approximately 2.25 hours post-dose, followed thereafter by a multiphasic decline (MVT-601-043). The terminal elimination half-life is 60.8 hours (TAK-385-1009). Upon once daily administration following a single loading dose of 320 or 360 mg on Day 1, steady state is achieved within 7 days (C27001, TB-AK160108) (**Table *4***).

Table 4. Summary of the Absorption, Distribution, Metabolism, and Excretion Properties of Relugolix

Absorption	
Absolute Bioavailability	11.6%
t_{max} (fasted)	2.25 h
Effect of Food (high-calorie/high-fat vs. fasting)	GMR (fed/fasted) and 90% CI of the $AUC_{0-\infty}$ 0.812 (0.644, 1.02)
Transporter(s) Involved in Relugolix Absorption	P-gp
Distribution	
Plasma Protein Binding (in vitro)	68.2% to 70.8% primarily to albumin
Blood: Plasma Ratio	0.78
Vss	3867 L
Metabolism	
Metabolic Pathways	In vitro CYP3A > CYP2C8, intestinal microflora
Elimination	
Primary Route of Elimination	Metabolism
Total Clearance (CL)	29.4 L/h
Renal Clearance (CL_r)	8.0 L/h
$t_{1/2}$ (effective)	25 h
$t_{1/2}$ (terminal)	60.8 h
% of dose excreted as total radioactivity (unchanged drug) in faeces	80.6 (4.2)
% of dose excreted as total radioactivity (unchanged drug) in urine	4.1 (2.2)

Abbreviations: $AUC_{0-\infty}$ = area under the curve from time zero extrapolated to infinity; CYP = cytochrome P450; GMR = geometric mean ratio; P-gp = P-glycoprotein; $t_{1/2}$ = half-life; t_{max} = time to maximum concentration; V_{ss} = volume of distribution at steady state.

Source: Table 28, Module 2.7.2

*** It should be noted that reported properties are based on the respective relugolix doses that were used in the clinical studies/data, which have not been adapted to the 120 mg dose.

Absorption

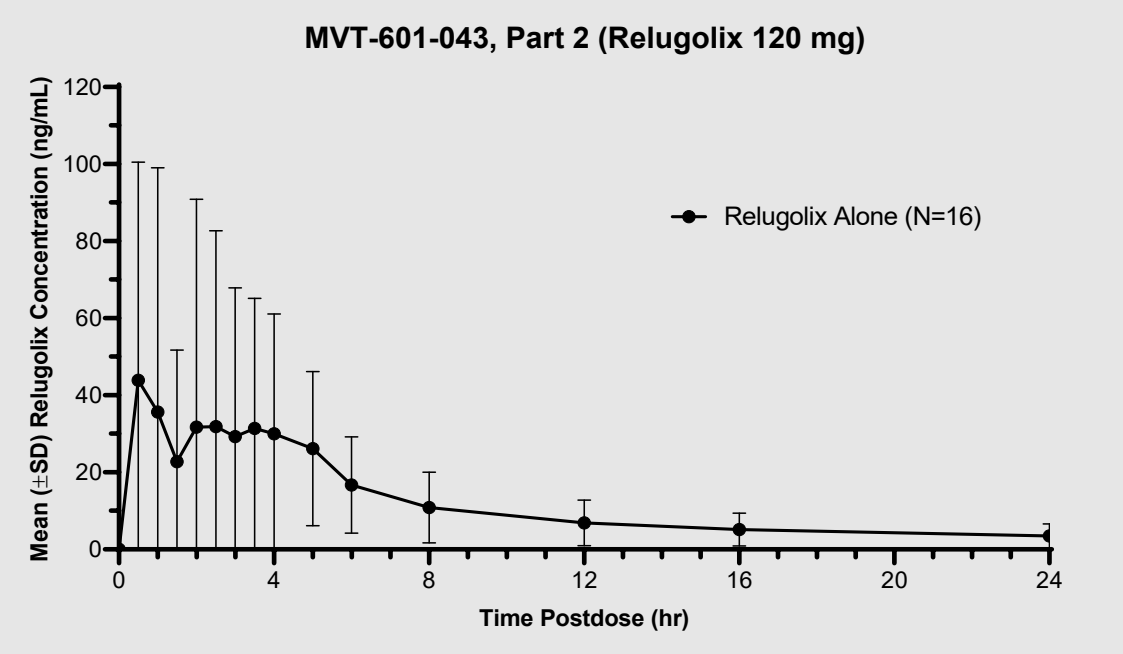
After administration of a single 120-mg dose of relugolix in the fasted state, relugolix is rapidly absorbed with multiple peaks observed in the relugolix concentration-time profiles. The first mean C_{max1} of 35.34 ng/mL is reached at a median t_{max1} of 2.25 hours (range 0.50 – 5.00 hours) and a second C_{max2} of 32.33 ng/mL is reached after a median t_{max2} of 3.50 hours (range 2.00-5.00). After reaching C_{max}, relugolix concentrations decline in a multi-phasic manner, initially with a rapid decrease in concentrations (between approximately 6 and 16 hours post-dose), followed by a slower decline (between approximately 12 and 24 hours post-dose) and subsequently by a slow terminal elimination phase characterized by a relatively flat slope (beginning at approximately 48 to 72 hours post-dose) with a terminal elimination half-life of approximately 60.8 hours. However, the majority of the total exposure to relugolix occurs within the first 24 hours after administration with little contribution to the overall AUC from the terminal portion of the elimination phase (**Figure 2**).

The estimated fraction absorbed is ~40% for a 80 mg dose based on the mass balance data, given that the preclinical data indicate that metabolite C can be formed in the intestinal flora (see below under Metabolism). As the absolute bioavailability at this dose was 11.6% (TAK-385-1009), there is a considerable first-pass effect. The absolute bioavailability of a single 120 mg oral dose of relugolix is estimated to be approximately 14% based on the greater than dose-proportional exposure of relugolix (calculated using the estimated dose effect on relative bioavailability [F1] in the PopPK model).

Relugolix reaches an initial peak by 0.5 hours post-dose followed by one or more subsequent absorption peaks until 5 hours post-dose. Because no secondary peaks were observed following intravenous administration of relugolix, it seems unlikely that enterohepatic recirculation of relugolix plays a major role. The absorption of relugolix seems to be strongly mediated by intestinal P-gp, because the bioavailability of 20 mg relugolix increased 6.2-fold when co-administered with erythromycin, which is a P-gp and moderate CYP3A4 inhibitor, whereas voriconazole (an inhibitor of CYP3A4) increased the exposure only 1.5-fold after a 40 mg relugolix dose.

Results from the erythromycin interaction study MVT-601-054 (see Drug Interactions), testing the effect of erythromycin on the bioavailability of 40 mg and 120 mg relugolix, have revealed that due to saturation of intestinal P-gp the inhibition effect of relugolix on intestinal P-gp decreases as the dose of relugolix is increased.

Figure 2. Mean (SD) Relugolix Plasma Concentration versus Time to 24 Hour Postdose after Administration of a Single 120-mg Dose of Relugolix in Healthy Male Participants



Formulation development for relugolix

Three relugolix formulations in multiple strengths (T2, T3, and T4B) were developed and administered in clinical studies supporting the prostate cancer indication. The 120-mg tablet strength of the T4B formulation is used in the pivotal phase 3 study.

Food effects

Concomitant intake of 120 mg relugolix (T4B) with a high-calorie, high-fat meal decreases the $AUC_{0-\infty}$ with 19% and C_{max} with 21% (TAK-385_1010). In the pivotal phase 3 study in men with advanced prostate cancer (MVT-601-3201), relugolix was administered on an empty stomach, at least 1 hour before or 2 hours after a meal. In this context, the intake with a high-calorie, high-fat meal represents the worst-case scenario and it can be expected that the decrease in relugolix exposure is less than 20%.

Distribution

Relugolix is bound to plasma proteins for 68 – 71%, primarily to albumin and to a lesser extent to α1-acid glycoprotein, in addition to other plasma proteins. The exposure to total radioactivity in whole blood was lower compared with that in plasma, indicating limited distribution into red blood cells (mean whole blood-to-plasma ratio of 0.78). The value for apparent volume of distribution at steady state of approximately 3900 L indicates that relugolix distributes widely into tissues.

Elimination

Based on study TAK-385-1009, in which a single 80-mg dose of [^{14}C]-relugolix was administered, total radioactivity in plasma was associated with a similar concentration-time profile with rapid absorption followed thereafter by a multi-phasic decline. The mean $t_{1/2}$ associated with the terminal elimination phase based on radioactivity was estimated to be 226 hours as a result of the very slow (flat) elimination of total radioactivity, particularly after 72 hours post-dose. The slower elimination of radioactivity might be due to slow release of relugolix from tissues, but also might be caused by metabolites with slow elimination.

The mean clearance after intravenous administration of an 80-µg dose of [^{14}C]relugolix was 29.4 L/hr (from absolute bioavailability study TAK-385-1009). Mean terminal elimination half-life based on plasma concentrations for relugolix is approximately 60 hours and the mean effective half-live ($t_{1/2, \text{eff}}$) is 25 hours.

Metabolism

In vitro metabolism

Three main metabolites were identified in *in vitro* studies with relugolix. Metabolite A (CYP3A4) and -B (CYP2C8) were formed in human liver microsomes. Further phenotyping demonstrated that the CYP enzymes contributing to the overall hepatic oxidative metabolism of relugolix were CYP3A4/5 (45%) > CYP2C8 (37%) > CYP2C19 (< 1%). The remaining 18% was mediated by other CYP enzymes or unevaluated biotransformation pathways. Another main metabolite, Metabolite C in faeces, is formed by intestinal microflora and likely represents unabsorbed relugolix.

In vivo metabolism in human subjects

Metabolite-C was identified as the major metabolite in human faeces, representing approximately 40% of the total radioactive dose. Metabolite-C was detected only at low levels in human plasma, likely from absorption of trace amounts after formation in the intestine.

Because Metabolite-A and Metabolite-B (combined) represent approximately 2.2% and 3.8% of total radioactivity in plasma in the 72-hour post-dose period after oral administration of a single 80-mg dose of [^{14}C]-relugolix in the human ADME study (TAK-385-1009), CYP3A4/5 and CYP2C8-mediated metabolism of relugolix are thought to be relatively minor pathways of systemic clearance *in vivo*.

The metabolic fate of relugolix is not entirely clear. Approximately half of the radioactivity in plasma, urine and faeces has not been identified, as 53% of radioactivity in plasma during first 72 hours after administration has been identified, 53% of radioactivity in urine and 56% of radioactivity in faeces, which is considerably lower than the 80% recommended in the guideline. However, multiple minor metabolites were detected in plasma, urine and faeces indicating that relugolix is extensively metabolised by various pathways.

Based on the fraction absorbed of ~40% and an absolute bioavailability of 11.6%, there is a considerable first-pass effect. Of the fraction escaping the first-pass metabolism, 19% is eliminated as

unchanged relugolix in the urine; hence, pre-systemic and systemic metabolism contribute approximately 70-80% to the elimination of an absorbed dose of relugolix.

Excretion

Recovery of radioactivity in the mass balance study was 87.1%, hence the collection period of 12 days is considered acceptable. The majority (82.7%) of radioactivity was recovered in faeces, with approximately 4.4% recovered in urine.

Approximately 2.2% of the total radioactive dose of relugolix is excreted unchanged in the urine and, based on an absolute bioavailability of 11.6%, an estimated 19% of an absorbed dose (i.e. following pre-systemic clearance) is excreted unchanged in the urine and 80% is eliminated through metabolism by multiple minor metabolic pathways and/or biliary secretion of unchanged drug. Approximately 38% of the administered dose is excreted as metabolites (other than Metabolite-C) in the faeces and urine. Metabolite-C, which is formed by intestinal microflora, is the primary metabolite in faeces (50.6%) and further reflects non-absorbed drug. However, the continuous excretion of radioactivity in the faeces beyond 72 hours after administration indicates that a substantial part (at least 40%) of relugolix is being absorbed and suggests a reasonably high first-pass effect, because the absolute bioavailability was only 11.6%.

Drug transporters

Relugolix has moderate intrinsic permeability in Caco-2 cells compared to the low and high permeability controls used. Relugolix is a substrate for P-gp.

As renal excretion of relugolix comprehends <25% of the absorbed fraction and as it is unlikely that enterohepatic recirculation contributes significantly to the exposure of relugolix, investigating if relugolix is a substrate for renal and/or bile transporters is considered not necessary.

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.

Dose proportionality and time dependency

Dose proportionality

Overall, the majority of the data demonstrate that the exposure to relugolix increases greater than dose-proportional after a single dose (60-360 mg) and at steady state after once dosing for 14 days (40-360 mg). The greater than dose-proportional increase in exposure to relugolix after a single dose is also supported by the PopPK model, wherein a covariate of 0.389 in the exponent was estimated for Dose ~ F1 in the dose range of 60 -160 mg.

Accumulation ratio

The accumulation of relugolix following once daily administration is approximately 2-fold; accumulation ratios for relugolix AUC_{0-T} were 2.07 to 2.21 and for C_{max} were 1.52 to 1.80. The accumulation for relugolix upon administration of 120-mg doses once daily is expected to be the same as that observed for 80- and 180-mg doses once daily. However, this accumulation upon once daily dosing of the same dose is less relevant after a loading dose of 360 mg.

After administration of 80-mg doses of relugolix once daily for 14 days, the mean $t_{1/2, eff}$ was 25 hours, indicating that the systemic exposure (in terms of AUC) to relugolix reduced by half in approximately 24 hours.

Attainment of steady state

Steady state of relugolix is reached not later than 7 days when a once daily doses of 60-80 mg is administered with a loading dose. The time to steady state is also reached not later than 7 days when a loading dose of 360 mg is administered on day 1 followed by a once daily dose of 120 mg.

Time dependency

No results on $AUC_{0-\tau}$ at steady state or $AUC_{0-\infty}$ after single dosing data, specifically at the 120 mg dose level, were available from the same study for assessment of time dependence.

Trough relugolix concentrations as measured every 4 weeks during the Phase 3 study MVT-601-3201 seem to be quite stable over time from 4 weeks until 48 weeks after dosing and indicate that the pharmacokinetics of relugolix is time independent for the 120 mg once daily dosing regimen.

Intra- and inter-individual variability

Relugolix 120 mg showed within-subject variability of 55 to 85% for AUC, and even higher variability for C_{max}, as determined from studies MVT-601-043 and TAK-385-1010. Relugolix can be considered a highly variable drug. Between-subject variability in exposure to relugolix after a single dose of 120 mg relugolix was also high, ranging from 80% to 130% for AUC higher and even for C_{max} (studies MVT-601-043 and TAK-385-1010). After multiple doses of 120 mg relugolix for 14 days, the between-subject variability in exposure to relugolix ranged from 51% to 109% for $AUC_{0-\tau}$, 85% to 154% for C_{max} and 43 to 88% for C_{trough} (studies MVT-601-044, MVT-601-045 and MVT-601-3201).

Variability of P-gp activity or expression level likely contributes to the high variability of relugolix, as the variability of relugolix decreased with >50% for C_{max} and $AUC_{0-\infty}$ when relugolix was co-administered with the P-gp and moderate CYP3A inhibitor erythromycin (studies TAK-385/CPH-010 and MVT-601-054). In line with this, the inter-subject variability in estimated mean plasma clearance (CL) of relugolix after intravenous administration was only 15% (study TAK-385_1009).

Pharmacokinetics in target population

In general there is an overlap in ranges of exposures between healthy men and men with prostate cancer, and the bigger groups do not indicate major differences in pharmacokinetics of relugolix (Table 5).

Table 5. Comparison of Plasma Relugolix Pharmacokinetics between Healthy Men and Men with Prostate Cancer

Arithmetic Mean (CV%)							
Relugolix 360 mg single/loading dose							
Healthy Men[a]				**Men with Prostate Cancer**			
Study (n)	$AUC_{0-\infty}$ (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	C_{max} (ng/mL)	Study (n)	$AUC_{0-\infty}$ (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	C_{max} (ng/mL)
Thorough QT/QTc Study (TAK-385_106) (n = 70)	1762 (57)	1374 (55)	253 (79)	Phase 1 Study in Men with Prostate Cancer (TB-AK160108) Part A Cohort 4 (n=3)	-	663 (75.7)	254 (130)
Prostate Cancer-Enabling Study (C27001) Part 1, Cohort 4 (n = 6)	1650 (43.3)	1440 (43.4)	194 (60.3)	Phase 3 Study (MVT-601-3201) Japanese subset (n=7)	-	985 (75.4)	215 (85.9)
Prostate Cancer-Enabling Study (C27001) Part 2, Cohort 3 (n = 6)	-	1876 (51.9)	489 (60.7)	-	-	-	-
120 mg once daily							
Healthy Men				**Men with Prostate Cancer**			
Study (n)	AUC_{0-24} (ng*hr/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)	Study (n)	AUC_{0-24} (ng*hr/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
Midazolam Interaction Study (MVT-601-044) (n = 12)	367 (67.9)	49.9 (75.9)	7.47 (70.5)	Phase 1 Study in Men with Prostate Cancer (TB-AK160108) Part A Cohort 2 (n = 3)	364 (80)	94.4 (122)	8.47 (69.4)
Rosuvastatin Interaction Study (MVT-601-045) (n = 12)	556 (56.0)	79.1 (63.3)	10.5 (49.6)	Phase 1 Study in Men with Prostate Cancer (TB-AK160108) Part A Cohort 4 (n = 3)	379 (52.7)	65.6 (62.3)	9.72 (51.6)
-	-	-	-	Phase 3 Study (MVT-601-3201) Japanese subset (n = 7)	407 (41.3)	70.2 (92.0)	10.7 (41.5)
-	-	-	-	Phase 3 Study (MVT-601-3201) All subjects (n = 603)	-	-	9.68 (91.9) (Week 5)

Abbreviations: AUC = area under the concentration-time curve; AUC_{0-24} = AUC from time 0 to 24 hours postdose; $AUC_{0-\infty}$ = AUC from time 0 extrapolated to infinity; C_{max} = maximum observed concentration; CSR = clinical study report; C_{trough} = concentration at the end of the dosing interval; n = number of participants included in statistical summary.

[a] All healthy participant data is from men, except study TAK-385_106, which included 36 (51%) men and 34 (49%) women.

Special populations (Intrinsic Factors)

The potential effects of intrinsic factors on exposure to relugolix, including demographic parameters (age, race, sex, body weight, renal impairment) were evaluated either in dedicated studies, by cross-study comparisons, or with the population pharmacokinetic analysis.

PopPK analysis

The selected clinical studies were appropriate to investigate the specified objectives of the population pharmacokinetic model. The pharmacokinetics of relugolix were best described by a three-compartment model with first-order absorption with lag-time and first-order elimination. Parameters appeared to be estimated with reasonably high precision.

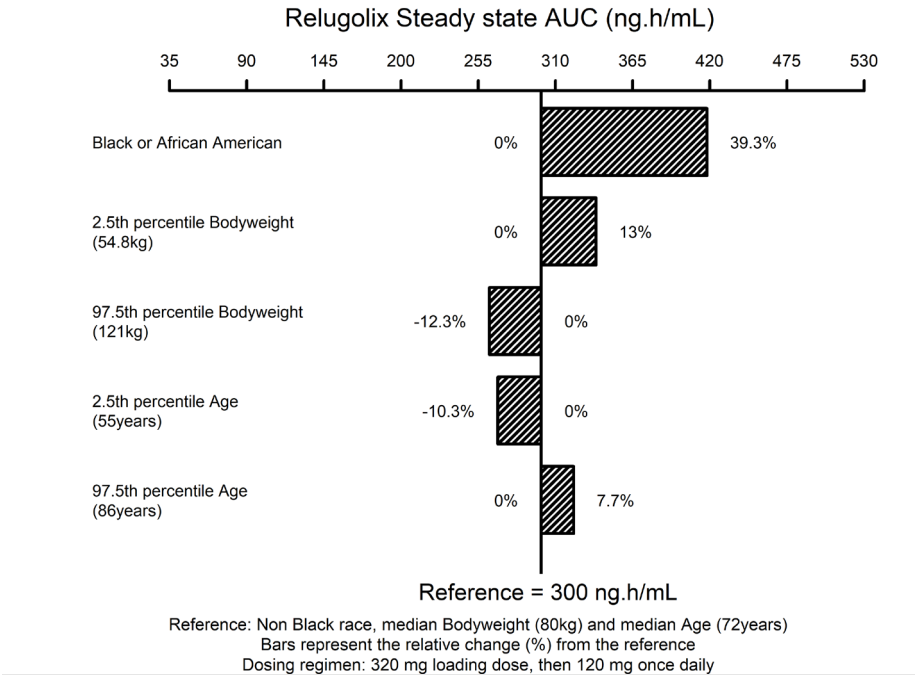
A relatively large interindividual variability on several model parameters was identified, predominantly in the absorption phase (160% on K_a) and distribution phase (123% on V_c/F), even after inclusion of several covariates. The large IIV values for Ka and V_c/F seem to be in line with the large variation seen in absorption from individual relugolix plasma concentration-time profiles and the large variation in the trough concentrations in the Phase 2 and Phase 3 studies. The identified covariates are in line with a previously conducted population pharmacokinetic analysis for Ryeqo (EMEA/H/C/005267). Stage of cancer was tested as a covariate in a separate, additional analysis (see below).

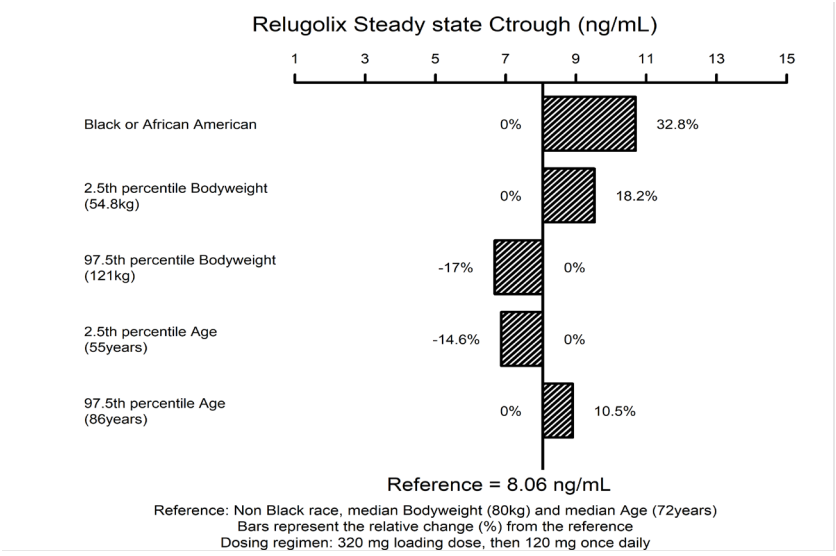
Body weight as a significant covariate on CL/F with the allometric exponent value of 0.32 was determined based on covariate evaluations for the pharmacokinetics of the analysis population, and was able to characterize the observed trend in CL with body weight within the dataset. This is acceptable as the primary purpose of the covariate analysis was to characterize the pharmacokinetics within the analysis population, not for purposes of extrapolation to lower or higher body weights, in which case a fixed exponent of 0.75 might have been considered.

The standard goodness-of-fit plots, the prediction-corrected visual predictive checks of both the development dataset and validation dataset indicate no clear structural deviations.

Using the final PopPK model simulations were done to predict the effects of covariates race and body weight on exposure to relugolix (in terms of model-predicted total exposure or trough concentrations at steady state [AUC_{ss}; $C_{trough,ss}$]. Overall, the predicted collective effects of covariates race and body weight were relatively modest and well within the comparability bounds of (0.50 to 1.50) for clinically meaningful changes in exposure (AUC and $C_{trough,ss}$) associated with the established safety and efficacy profile for relugolix (**Figure 3**).

Figure 3. Impact of PopPK Covariates on Relugolix Steady-state AUC_{ss} and $C_{trough,ss}$





Abbreviations: AUC = area under the concentration-time curve; AUC_{ss} = AUC over a dosing interval at steady state; $C_{trough,ss}$ = concentration at the end of the dosing interval at steady state.

Source: Figure 11, Figure 12, PopPK report

Health status / Stage of cancer

Neither health status ("healthy" and "prostate cancer patients") nor stage of cancer, based on the Tumor-Node-Metastasis stages captured at baseline in each prostate cancer patient ("localized", "locally advanced", "metastatic", "not classifiable", and "missing"), were identified as a statistically significant covariate in the population PK and PK/PD analyses. A separate, additional covariate check was done for this.

Age / elderly /children

Of the 1530 study participants from all clinical studies with relugolix pharmacokinetic data available, a total of 432 (28.2%) were 65-74 years of age, 307 (20.1%) were 75-84 years of age, and 39 (2.5%) were ≥ 85 years of age.

No children (<18 yrs of age) have been dosed with relugolix so far.

Race

Black/African-American race was identified as a significant covariate in the PopPK model on the CL/F and Vc/F. Simulation for the pivotal phase 3 study MVT-601-3201 showed that Black/African American men had approximately 39% higher AUC_{ss} and 33% higher $C_{trough,ss}$ of relugolix compared with non-Black/African American men. However, this effect was reduced in a simulated population of 10,000 individuals to 26% and 16% increase in AUC_{ss} and $C_{trough,ss,}$ respectively.

Sex / gender

There is no major difference in exposure to relugolix between men and women, according to the results of study TAK-385/CPH-010 wherein pharmacokinetic data were described separately for both sexes.

Body weight

Body weight was identified as a significant covariate on CL/F of relugolix in the final PopPK model. However, impact of body weight on relugolix AUC_{ss} and $C_{trough,ss}$ was small, with median differences < 15% between patients above and below the median weight of 80 kg in the simulation of the pivotal phase 3 study MVT-601-3201.

Renal impairment

Based on the dedicated renal impairment studies with 40 mg relugolix, the exposure to relugolix (AUC_{0-t}) increased 1.5-fold in subjects with moderate and 2.0-fold in subjects with severe renal function. The terminal $t_{1/2}$ is not affected in the subjects with renal impairment and only 19% of the absorbed relugolix is excreted via the renal pathway.

The effect of renal function (creatinine clearance) on the relugolix exposure (post-hoc estimates of AUC_{ss} and $C_{trough,ss}$ based on the PopPK model) in the pivotal phase 3 study MVT-601-3201 were analysed and quantified, where the actual dose of 120 mg was administered.

In this study, 148 patients were included with moderate renal impairment, including 4 patients with baseline creatinine clearance values just below 30 ml/min (severe renal impairment). The results from the simulations using the phase 3 population confirm the results for the dedicated renal impairment studies with 40 mg relugolix, i.e. similar exposure in patients with mild renal impairment and 1.4-fold higher exposure in subjects with moderate renal impairment as compared to patients with normal renal function.

Hepatic impairment

After administration of a single 40 mg dose of relugolix to patients with mild or moderate hepatic impairment, no clinically meaningful effects on the rate or extent of absorption of relugolix were observed, although small numerical differences in the exposure-related pharmacokinetic parameters were noted. In patients with mild hepatic impairment total exposure to relugolix was decreased by 31% and in patients with moderate hepatic impairment exposure was decreased by 5%, compared with healthy participants with normal hepatic function. These slight decreases are probably more a reflection of the large between-subject variability and the small group size (as noted before) than a true effect. The terminal elimination $t_{1/2}$ estimates were nearly the same (52, 51, and 49 hours) in

patients with mild or moderate hepatic impairment and healthy participants with normal hepatic function, respectively.

Extrinsic Factors / Drug Interactions

The clinical pharmacology program for Orgovyx consisted of seven drug interaction studies, five of which assessed the impact of other drugs on relugolix (victim interactions: TAK-385/CPH-010, C27005, MVT-601-043, MVT-601-1004, MVT-601-054) and two that assessed the effect of relugolix on other drugs (perpetrator interactions: MVT-601-044, and MVT-601-045).

In vitro: Effect of Other Drugs on Relugolix (Victim Interactions)

Relugolix is a substrate for the P-gp efflux transporter responsible for the limited oral bioavailability (11.6%) and the absorption-related drug interactions due to P-gp inhibition or induction. Although a minor pathway in vivo, in vitro data showed that CYP3A4 is responsible for 45% of CYP-mediated metabolism, and therefore the potential effects of P-gp and/or CYP3A4 inhibitors or inducers on the pharmacokinetics of relugolix were clinically studied (Victim Interactions).

In vitro: Effect of Relugolix on Other Drugs (Perpetrator Interactions)

In pooled human liver microsomes, relugolix was not a direct inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6, nor was there a time-dependent inhibition of any CYP enzyme, including CYP3A4/5. However, based on in vitro studies, relugolix has the potential for CYP3A4/5-mediated drug interactions due to induction (relugolix induced CYP3A4 mRNA expression in human hepatocytes in a concentration-dependent manner at concentrations ≥ 1 µM) or direct inhibition (relugolix inhibited midazolam 1'-hydroxylase activity with an IC_{50} value of 16 µM).

Based on the exposure associated with the proposed clinical dose of 120 mg once daily, results from the in vitro studies indicate that relugolix has the potential to interact with intestinal CYP3A, and therefore a drug interaction study with midazolam, a sensitive CYP3A4 substrate, was conducted (MVT-601-044).

For CYP2B6, the lowest concentration of relugolix that resulted in a positive in vitro CYP2B6 mRNA induction signal was observed at ≥ 3 µM relugolix, which is at least 73-fold higher than the unbound C_{max} for relugolix based on oral doses of 120 mg QD ($C_{max,u,ss}$ 41 nM). Taken together with the weak clinical induction of CYP3A by relugolix at 120 mg QD, the potential for clinically meaningful induction of CYP2B6 is unlikely.

In vitro studies demonstrated that relugolix was not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or BSEP at the concentrations tested, but relugolix inhibited transport by P-gp, BCRP, MATE1, and MATE2-K. Based on in vitro inhibitory potencies and estimated relugolix exposures associated with administration of 120-mg doses of relugolix once daily, there is potential for relugolix to inhibit intestinal BCRP based on thresholds defined in the agency guidelines for drug interactions (for a 120-mg dose, the I_{gut}/IC_{50} value was 30.9, marginally exceeding the recommended threshold of 10, indicating potential for a clinically meaningful drug interaction with intestinal BCRP. Therefore, for BCRP a clinical drug-drug interaction study with rosuvastatin, a substrate for the BCRP efflux transporter, was conducted (MVT-601-045).

The projected I_{gut} concentration based on a 120 mg dose of relugolix (770 µM) results in an I_{gut}/IC_{50} value of 12.6 for P-gp, suggesting that a clinically-relevant interaction with P-gp substrates may be possible. Since the more than dose proportional increase in relugolix exposure suggests saturation of P-gp with increasing doses, a clinical DDI study with a P-gp substrate such as dabigatran etexilate or fexofenadine is required for the 120 mg dose of relugolix. Such DDI study is already a post-approval commitment for the Ryeqo application for the 40 mg relugolix dose and will also include an arm with the 120 mg dose of relugolix.

In vivo: Effect of Other Drugs on Relugolix (Victim Interactions)

The potential effects of P-gp and/or CYP3A inhibitors or inducers on the pharmacokinetics of relugolix were assessed in four dedicated clinical pharmacology studies. The selection of specific inhibitors and inducers facilitated a better understanding of the relative contribution from P-gp and CYP3A mediated effects.

A summary of the results from the clinical DDI studies on the effects of coadministered drugs on relugolix PK is presented in **Table 6**.

Table 6. Summary of the Effects of Coadministered Drugs on Relugolix PK

Coadministered Drug and Regimen (Mechanism of Interaction)	Relugolix Dose	N	Geometric Mean Ratio (90% CI) of Relugolix Pharmacokinetic Parameters with/without Co-administered Drug (No Effect = 1.00)		Clinical Recommendation
			C_{max}	$AUC_{0-\infty}$	
Erythromycin 300 mg four times daily for 7 days (P-gp and Moderate CYP3A Inhibitor, study TAK-385/CPH-010)	20 mg SD	20	6.18 (4.75, 8.04)	6.25 (5.31, 7.35)	The concomitant use of relugolix with a P-gp inhibitors should be avoided. If co-administration is necessary, take relugolix first and separate dosing by at least 6 hours for P-gp inhibitors with a once or twice daily dosing regimen. Alternatively, treatment with relugolix may be interrupted for up to two weeks if a short course of treatment with a P-gp inhibitor with dosing regimen of more than twice daily is required.
Erythromycin 500 mg four times daily for 12 days (P-gp and Moderate CYP3A Inhibitor, study MVT-601-054)	40 mg* SD	16	3.82 (2.94, 4.97)	4.06 (3.24, 5.09)	See above.
Erythromycin 500 mg four times daily for 12 days (P-gp and Moderate CYP3A Inhibitor, study MVT-601-054)	120 mg SD	27	2.89 (1.98, 4.21)	3.53 (2.58, 4.84)	See above.
Rifampin 600 mg once daily for 12 days (Combined P-gp and Strong CYP3A Inducer, study MVT-601-1004)	40 mg SD	18	0.77 (0.56, 1.06)	0.45 (0.34, 0.62)	The concomitant use of relugolix with a combined P-gp and strong CYP3A inducers should be avoided. If coadministration is necessary, adjust the dose of relugolix to 240 mg once daily.
Atorvastatin 80 mg once daily for 9 days (Weak CYP3A Inhibitor, study C27005)	40 mg SD	20 [a]	0.78 (0.51, 1.18)	0.95 (0.77, 1.17)	No dose adjustment
Fluconazole 400 mg once daily for 1 day followed by 200 mg once daily for 8 days (Moderate CYP3A Inhibitor, study C27005)	40 mg SD	20	1.44 (1.13, 1.83)	1.19 (1.06, 1.33)	No dose adjustment
Voriconazole 400 mg Q12H for 1 day followed by 200 mg Q12H for 11 days (Strong CYP3A Inhibitor, study MVT-601-043)	40 mg SD	13	1.21 (0.92, 1.59)	1.51 (1.25, 1.83)	No dose adjustment
Voriconazole 400 mg Q12H for 1 day followed by 200 mg Q12H for 11 days (Strong CYP3A Inhibitor, study MVT-601-043)	120 mg SD	14	0.82 (0.43, 1.57)	1.12 (0.68, 1.84)	No dose adjustment

Abbreviations: Q12H = every 12 hours; SD = single dose.
[a] N = 19 for $AUC_{0-\infty}$.
*Administered as the fixed-dose combination tablet (relugolix/E2/norethindrone acetate [40 mg/1 mg/0.5 mg])

In vivo: Effect of Relugolix on Other Drugs (Perpetrator Interactions)

Based on in vitro data, dedicated clinical pharmacology studies to assess the potential effect of relugolix on midazolam, a sensitive CYP3A4 substrate (MVT-601-044) and rosuvastatin, a BCRP substrate (MVT-601-045) were considered necessary. In the two studies, the potential effects of both a

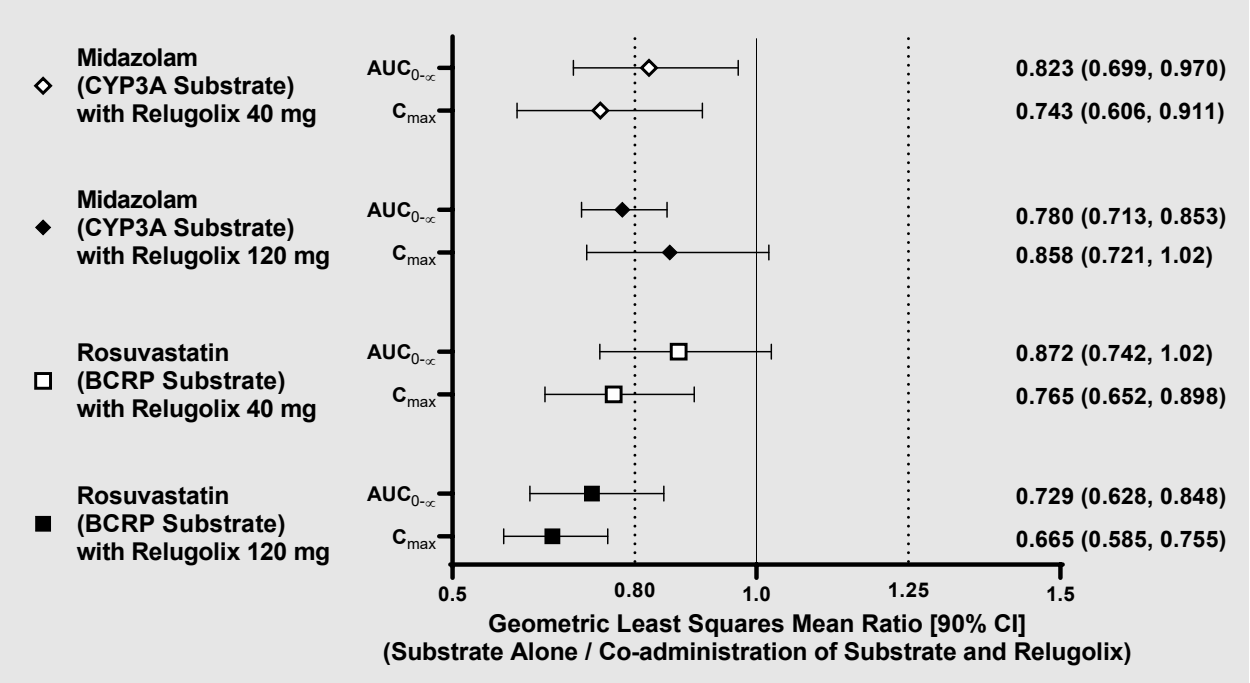
40- and 120-mg dose of relugolix were evaluated in Part 1 and Part 2 of each study, respectively, considering that potential inhibition and/or inductive effects are dose (concentration)-dependent.

Results from the midazolam interaction study (MVT-601-044), in which a single 5-mg dose of midazolam was co-administered with a 40-mg (Part 1) or a 120-mg (Part 2) dose of relugolix following once daily administration of respective doses of relugolix for 14 days, showed that the potential inductive and/or inhibitory effects of relugolix on CYP3A4-mediated metabolism of midazolam, a sensitive CYP3A4 substrate, are slight and do not appear to be dose dependent (**Figure 4**).

Results from the rosuvastatin interaction study (MVT-601-045), in which a single 10-mg dose of rosuvastatin was co-administered with a 40-mg (Part 1) or a 120-mg (Part 2) dose of relugolix following once daily administration of respective doses of relugolix for 14 days, showed a small decrease in exposure to rosuvastatin, a BCRP efflux transporter, that appeared to have a dose-related effect (**Figure 4**).

Overall, upon co-administration with relugolix, the total exposure ($AUC_{0-\infty}$) to rosuvastatin decreased with a trend toward a dose-related effect (13% reduction for 40 mg dose and 27% reduction for 120-mg dose of relugolix).

Figure 4. 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.

Effect of Mixed-Mechanism Perpetrator Enzalutamide

Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway, also used for treatment of prostate cancer. The SmPC of Xtandi (enzalutamide) mentions that enzalutamide is a strong CYP3A inducer and may also be an inducer of

P-gp, Also, there is some indication that enzalutamide may be an inhibitor of P-gp as well. This is comparable to the effects of rifampin.

For all study participants included in study MVT-601-3201, treatment with relugolix was initiated as monotherapy. In 20 patients, whose disease progressed during the study, enzalutamide was prescribed in accordance with prostate cancer treatment guidelines, in combination with relugolix for a mean of 113 days. During treatment with relugolix alone, combination therapy with enzalutamide < 30 days and combination therapy with enzalutamide > 30 days, mean relugolix trough concentrations in plasma were 9.6, 11.9 and 10.2 ng/mL, respectively. Corresponding values for testosterone predose concentrations in serum were 10.1, 12.5 and 15.7 ng/dL, respectively, demonstrating sustained therapeutic suppression of testosterone concentrations during combination therapy with relugolix and enzalutamide.

Drug-drug Interaction Potential for Drugs Effecting Gastric pH

Based on the solubility profile of relugolix, a 360-mg dose (recommended loading dose) and a 120-mg dose (recommended daily dose) of relugolix will completely dissolve *in vivo* at or below pH 5.2 and pH 5.6, respectively. Thus, relugolix is highly soluble at typical gastric (stomach) pH and absorption of relugolix is unlikely to be limited by solubility or dissolution under the conditions typically observed in the upper gastrointestinal tract. Thus, relugolix dissolution may be pH sensitive.

2.6.2.2. Pharmacodynamics

The pharmacodynamic effects of relugolix were evaluated after single and multiple dose administrations in healthy male subjects (study C27001). A thorough QT/QTc Study has been performed, which has been previously reflected in the initial MA for Ryeqo (see Ryeqo EPAR). An overview of these studies is presented in the table below:

Table 7. Studies including pharmacodynamics

Study (Region)	Short Title	Relugolix Dose(s) (mg)	Fasting Condition	Number of Male/Female Participants
Single and Multiple Rising-Dose Studies				
C27001 (UK) Module 5.3.3.1	Safety and Tolerability, Pharmacokinetic and Pharmacodynamic Study in Healthy Men (Prostate Cancer-Enabling Study)	Part 1 (SD): 80, 120, 180, 360, placebo Part 2 (once daily x 14 days): 80, 180, 360/40, 320/240/160/20, 320/160/20, placebo Part 3 (once daily x 28 days): 160, 320/160/40, placebo Part 4 (once daily x 28 days): 60, 80, placebo	Part 1: Fasted (8 hr before, 4 hr after) + Fed (Cohort 3) Parts 2, 3, 4: Drug administered 30 min before meal	174/0 (126 relugolix, 48 placebo)
Pharmacodynamic Studies - secondary pharmacology				
TAK-385_106 (US) Module 5.3.4.1	Thorough QT/QTc Study	• 60 mg SD • 360 mg SD • placebo • moxifloxacin	Fasted (10 hr before, 4 hr after)	60 mg: 36/34 360 mg 36/34
Pharmacokinetic and Pharmacodynamic Modelling				
MYOV-PMX-RELUGOLIX-1816 Report 01 + Addendum 01-04 Module 5.3.4.2	Population Pharmacokinetic/ Pharmacodynamic (PopPK/PD) Analyses	Various	Various	999/0

Abbreviations: PopPK/PD = population pharmacokinetic/pharmacodynamic; SD = single dose; UK = United Kingdom; US = United States.

Mechanism of action

Relugolix (previously known as TAK-385 and T-1331285) is an orally active, nonpeptide gonadotropin-releasing hormone (GnRH) receptor antagonist that competitively binds to GnRH receptors in the anterior pituitary gland, which blocks endogenous GnRH signaling and prevents the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland with a resultant decrease in the production of the sex steroid hormones, including testosterone from the testes. After oral administration of relugolix, a rapid and reversible, dose-dependent decrease in LH and FSH concentrations is observed, with corresponding decreases in systemic testosterone concentrations.

Primary pharmacology

The single- and multiple-rising dose study (C27001) was a double-blind, randomized, placebo controlled, 4-part study to assess the safety and tolerability, pharmacokinetics, and testosterone lowering efficacy of relugolix in healthy adult men. This study was conducted in the United Kingdom. Overall, a total of 176 male participants of which 171 participants completed the study across all study parts.

Dosing comprised of single 80-, 120-, 180-, or 360-mg dose of relugolix and multiple 20-, 40-, 80-, or 180 mg doses of relugolix once daily for 14 days or 40-, 60-, 80- or 160-mg doses of relugolix once daily for 28 days.

- In Part 1 (SD), In-patient: 80, 120, 180, 360, placebo, 32 male participants, aged 18 to 50 years
- In Part 2, (once daily x 14 days), In-patient: 80, 180, 360/40, 320/240/160/20, 320/160/20, placebo, 40 male participants, aged 40 to 70 years
- In Part 3, (once daily x 28 days), Outpatient: 160, 320/160/40, placebo, 66 male participants, aged 45 to 75 years
- In Part 4, (once daily x 28 days), Outpatient: 60, 80, placebo, 38 male participants aged 45 to 75 years

Study objectives

- To evaluate the effect on testosterone and luteinizing hormone (LH) of TAK-385 in healthy male subjects following a single and multiple dose.
- To assess the effect of a single and multiple dose of TAK-385 on serum DHT and FSH
- To identify the dose range across which medical castration (average testosterone levels < 0.69 nmol/L) occurs during the second week of dosing
- To evaluate the safety and tolerability of 1 or more dose levels of TAK-385 achieving maximal suppression of testosterone in men receiving an oral GnRH antagonist
- To confirm 1 or more TAK-385 dose levels that achieve sustained medical castration during the final 2 weeks of dosing
- To evaluate the PK of TAK-385 in healthy male subjects following multiple dosing and to relate PK to hormone PD responses (PK/PD)

PD parameters

In Part 1 (single dose), blood samples for determination of testosterone, LH, FSH, and dihydrotestosterone (DHT) serum concentrations were collected pre-dose and at prespecified timepoints up to 48 hours post-dose.

In Part 2 (14 days dosing), blood samples for determination of testosterone, LH, FSH, and DHT serum concentrations were collected pre-dose and at prespecified timepoints up to 24 hours post-dose (Day 1) and pre-dose and at prespecified timepoints up to 48 hours post-dose (urine collected up to 24 hours post-dose) (Day 14). Blood samples for determination of testosterone, LH, FSH, and DHT serum concentrations were collected pre-dose on certain days between Day 3 and Day 13.

In Part 3 and Part 4 (28 days dosing), Day 1 and Day 28, blood samples for the determination of testosterone and LH serum concentrations were collected pre-dose and at prespecified timepoints up to 24 hours post-dose; additional samples were collected 672 hours after the last dose on Day 28 and pre-dose on Days 7, 14, and 21. Blood samples for determination of FSH, DHT, and insulin-like growth factor 1 serum concentrations were collected pre-dose on Days 1, 14, and 28.

Serum testosterone was assayed using a conventional immunoassay for screening (LLOQ = 0.4 nmol/L). A validated LC/MS/MS method, with an LLOQ of 0.173 nmol/L and a ULOQ of 10.425 nmol/L, was used for all subsequent baseline and post-dose measurements.

Safety parameters

Safety was assessed throughout the study by repeated clinical and laboratory evaluations including physical examinations, clinical laboratory tests, vital sign measurements, ECGs (12-lead) and monitoring of adverse events.

Pharmacodynamic results

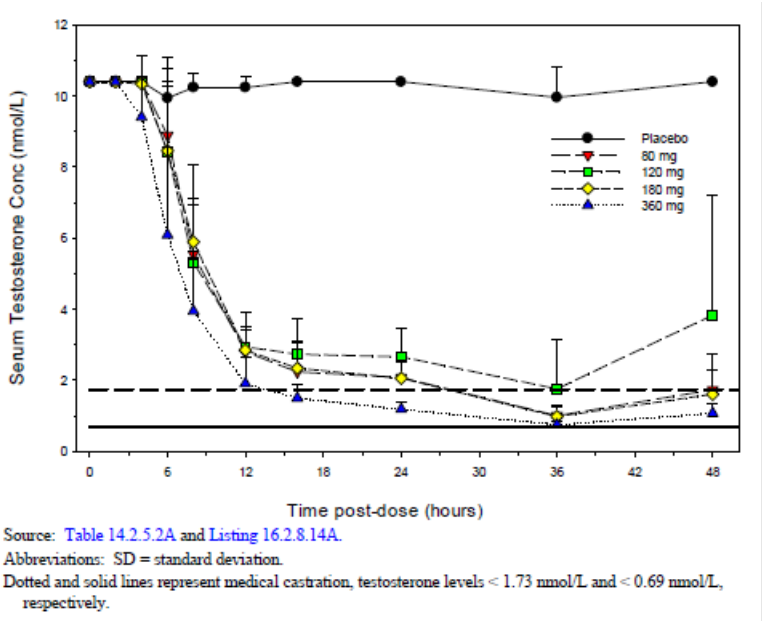
<u>Part 1, single dose: 80, 120, 180, 360, placebo:</u>

Testosterone

For participants receiving 80-, 120-, 180-, and 360-mg single doses of relugolix, mean serum testosterone concentrations decreased 4 to 6 hours post-dose to a nadir at 36 hours, then increased at 48 hours (

Figure 5). Relugolix 360 mg was associated with the most rapid and pronounced decrease in testosterone compared with the lower doses.

Figure 5. Mean (SD) Time-Course of Serum Testosterone Lowering Following Single Oral Dose Administration of TAK-385, Part 1



Source: Table 14.2.5.2A and Listing 16.2.8.14A.
Abbreviations: SD = standard deviation.
Dotted and solid lines represent medical castration, testosterone levels < 1.73 nmol/L and < 0.69 nmol/L, respectively.

Luteinizing hormone (LH)

After single dose, mean serum LH concentrations were lower in the 360-mg dose cohort than in the other 3 dose cohorts at the corresponding timepoints; however, baseline was also lower for the 360 mg dose group.

Follicle stimulating hormone (FSH) and dihydrotestosterone (DHT)

Mean serum FSH and DHT concentration profiles were similar across their respective dose cohorts at corresponding time points for the 80-, 120-, 180-, and 360-mg groups. Mean serum FSH concentrations began to decrease 2 hours post-dose to a low at 48 hours.

Mean serum DHT concentrations began to decrease 2 hours post-dose. Decreases in DHT were more profound in the 180 and 360-mg dose cohorts, with minor and variable further reductions occurring after the 12-hour time point.

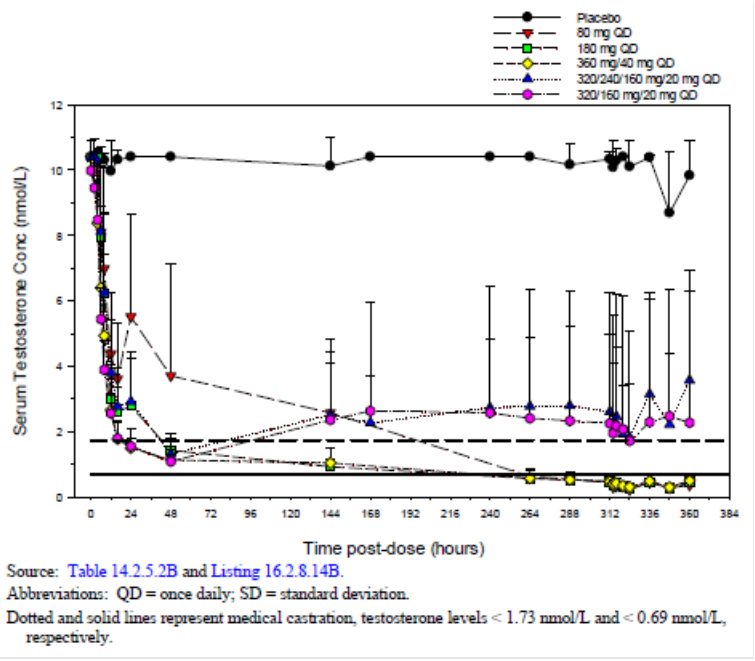
Part 2, multiple dose (once daily x 14 days: 80, 180, 360/40, 320/240/160/20, 320/160/20, placebo):

Testosterone

In Part 2, 1 to 3-day loading dose regimens of relugolix and relugolix 180 mg once daily (without a loading dose) resulted in rapid reductions in serum testosterone concentrations over the first 24 hours following the start of dosing (

Figure 6). Profound castrate levels (average testosterone concentrations < 0.69 nmol/L [< 20 ng/dL]) were achieved with repeat dosing for 14 days at daily maintenance doses of 40, 80, and 180 mg. The 20 mg once daily was insufficient in maintaining adequate suppression of testosterone concentrations during the second week.

Figure 6. Mean (SD) Time-Course of Serum Testosterone Lowering Following Multiple Oral Dose Administration of TAK-385 for 14 Days, Part 2



Source: Table 14.2.5.2B and Listing 16.2.8.14B.
Abbreviations: QD = once daily; SD = standard deviation.
Dotted and solid lines represent medical castration, testosterone levels < 1.73 nmol/L and < 0.69 nmol/L, respectively.

Luteinizing hormone (LH)

Regardless of loading dose regimen, 20 mg once daily was insufficient in maintaining adequate suppression of serum LH concentrations during the second week.

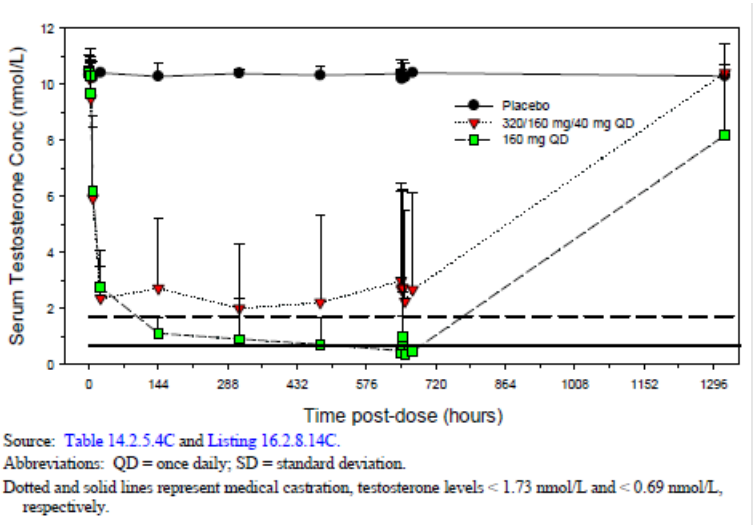
Part 3, multiple dose once daily (28 days: 160, 320/160/40) - Part 4 (once daily x 28 days: 60, 80, P):

Testosterone

In dosing for 28 days, both 160-mg (Part 3) and 80-mg (Part 4) doses of relugolix were effective at achieving castrate levels (< 1.73 nmol/L [< 50 ng/dL]) and profound castrate levels (< 0.69 nmol/L [< 20 ng/dL]) during the third and fourth weeks of repeat administration, whereas, there was more variability in response with 60 mg once daily. The 40-mg once daily dose of relugolix was ineffective in maintaining castrate levels between Days 14 and 28, despite use of a loading dose (see

Figure **7** Part 3 and Figure 8 Part 3 + Part 4).

Figure 7. Mean (SD) Time-Course of Serum Testosterone Lowering Following Multiple Oral Dose Administration of TAK-385 for 28 Days, Part 3

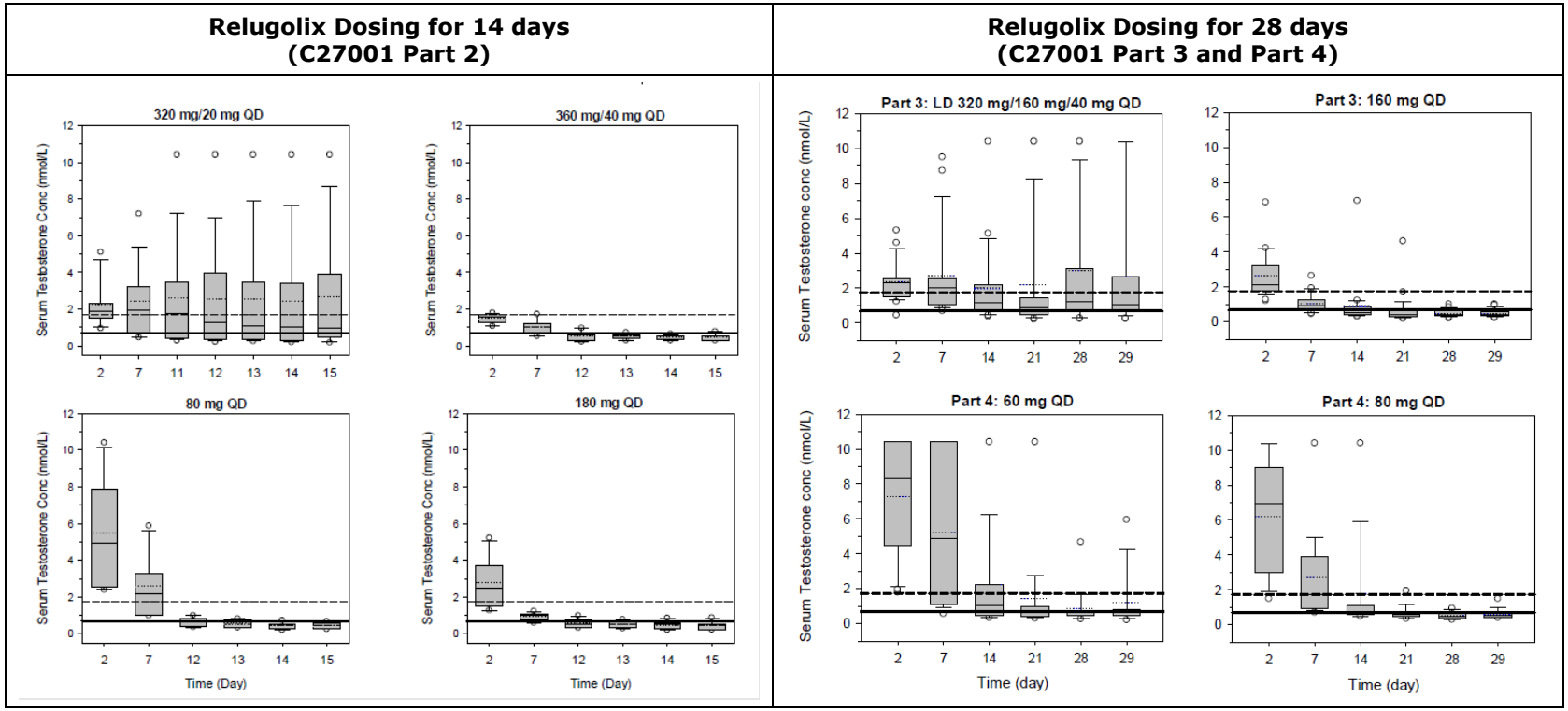


Source: Table 14.2.5.4C and Listing 16.2.8.14C.
Abbreviations: QD = once daily; SD = standard deviation.
Dotted and solid lines represent medical castration, testosterone levels < 1.73 nmol/L and < 0.69 nmol/L, respectively.

Exploratory PK-PD correlation

Sustained, lower-threshold medical castration of < 0.69 nmol/L was consistently achieved at doses of 80, 160, and 180 mg TAK-385. Consistent with the observed dose-dependent suppression of testosterone across the 20 to 180-mg QD studied dose range, the magnitude of the testosterone lowering-response was correlated with individual TAK-385 plasma trough concentrations; the higher the TAK-385 systemic exposure, the greater the number of subjects achieving and maintaining medical castration throughout the treatment period. Median TAK-385 trough concentrations of > 4 ng/mL, which were associated with maintenance doses of 80 mg or greater, reduced testosterone to below conventional castration levels of 1.73 nmol/L in all subjects, with the majority having serum testosterone levels decreased to below the lower castration threshold of 0.69 nmol/L after 28 days of treatment with TAK-385.

Figure 8. Serum Testosterone Concentrations Over Time after Administration of 20-, 40-, 60-, 160- or 180-mg Doses of Relugolix (± a Loading Dose) Once Daily for 14 or 28 Days.



Abbreviations: conc = concentration; LD = loading dose; QD = once daily.

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.

Part 2 Once daily administration of a 20-mg dose was preceded by loading doses of either 320/240/160 mg (Cohort 4) or 320/160 mg (Cohort 5).

Source: Figure 11-8 (Table 14.2.5.2B), Figure 11-10 (Table 14.2.5.4C), C27001 CSR.

Safety summary

Single 80-, 120-, 180-, or 360-mg dose of relugolix and multiple 20-, 40-, 80-, or 180 mg doses of relugolix once daily for 14 days or 40-, 60-, 80- or 160-mg doses of relugolix once daily for 28 days were generally safe and well tolerated in healthy adult men. Most commonly reported drug-related AEs included bradycardia, headache, and hot flush.

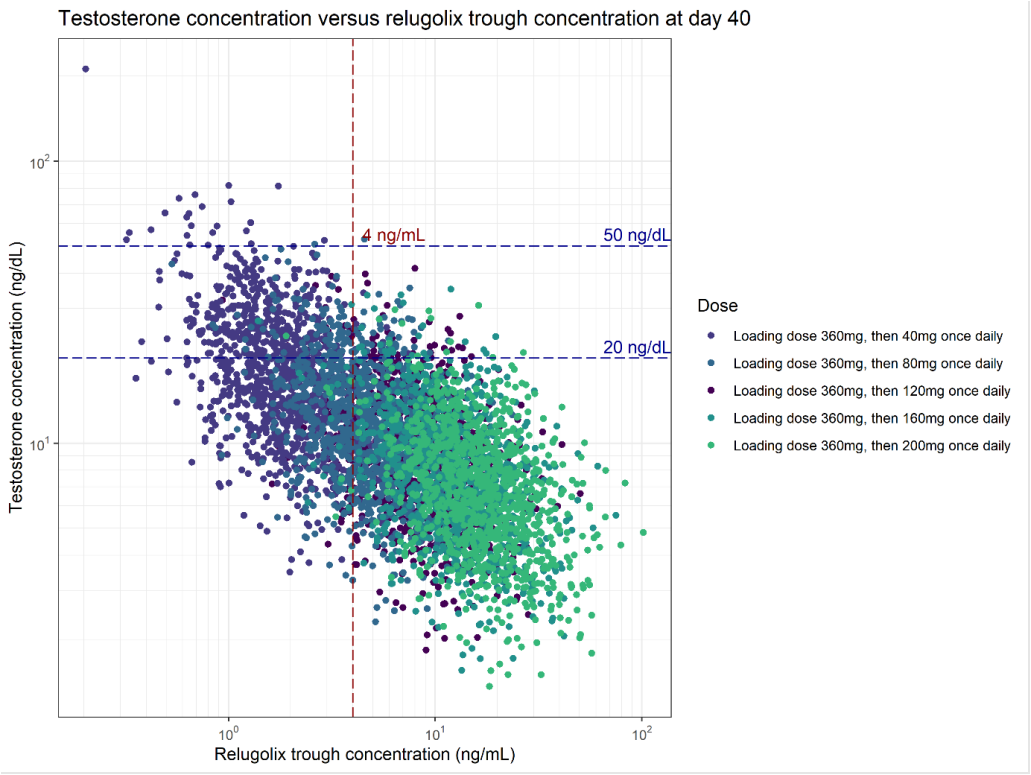
- Reversible transaminase elevations (ALT and AST) that reached ≥ 3 × ULN, considered to be an adverse event of clinical interest, that led to study discontinuation, were observed in two participants. Additionally, one participant was also discontinued from the study due to reversible transaminase elevations (ALT and AST) that did not meet the criteria for an adverse event of clinical interest (ie, maximum values were < 3 × ULN). For all three participants, total bilirubin remained within the normal range throughout the study.

Relationship between plasma concentration and effect

A sequential approach was used to develop a semi-mechanistic population PK/PD model. The model was based on a previous study by Romero et al., but modified to allow for the quantification of the antagonistic properties of relugolix and the absence of data for GnRH and the receptor. Endogenous GnRH and the receptor were modelled by conditioning on the changes in testosterone over time. A more simple empirical direct or indirect response model could probably be also applied to quantify the pharmacodynamics over testosterone. However, the semi-mechanistic model is adequate in describing the testosterone concentrations over time and is most likely a more accurate reflection of the systems biology.

The relationship between testosterone concentrations and relugolix C_{trough} supports that the 120-mg dose of relugolix is the minimum maximally-effective dose (Figure 9). In the pivotal phase 3 study in men with advanced prostate cancer (MVT-601-3201) a mean relugolix C_{trough} of 9.68 ng/mL was observed (Table 5), and based on the relationship between testosterone concentration and relugolix C_{trough}, this value is strongly associated with testosterone concentrations at castrate levels (< 1.73 nmol/L [< 50 ng/dL]) and profound castrate levels (< 0.69 nmol/L [< 20 ng/dL]) (Figure 9). This figure also illustrates that the cut-off of 4 ng/mL as a target relugolix trough concentration, suggested previously during relugolix development program, appears to be appropriate to achieve castrate levels (< 50 ng/dL) in the majority of patients.

Figure 9. PopPK/PD Model-Simulated Testosterone Concentration versus Relugolix C_{trough}



Notes: Relugolix was administered for 40 days to show relationship between steady-state testosterone concentration and relugolix plasma C_{trough}.
Testosterone concentrations of < 50 ng/dL (< 1.73 nmol/L) and < 20 ng/dL (< 0.69 nmol/L) represent castrate levels and profound castrate levels, respectively.
Source: Figure 29, MYOV-PMX-RELUGOLIX-1816 Report 01.

Comparability Bounds

Comparability bounds are devised during clinical development of a new chemical entity based on the evolving safety and efficacy profile that defines the therapeutic window, with the upper and lower thresholds representing clinically meaningful changes in drug exposures with respect to safety and efficacy, respectively. The lower comparability bound represents the degree to which drug exposures may decrease without compromising efficacy and is typically based on the exposure-response profile specific to a particular compound. The upper comparability bound represents the degree to which drug exposures may increase without increasing the risk for experiencing safety-related events and is typically based on the clinical safety profile associated with doses or exposures above the recommended clinical dose.

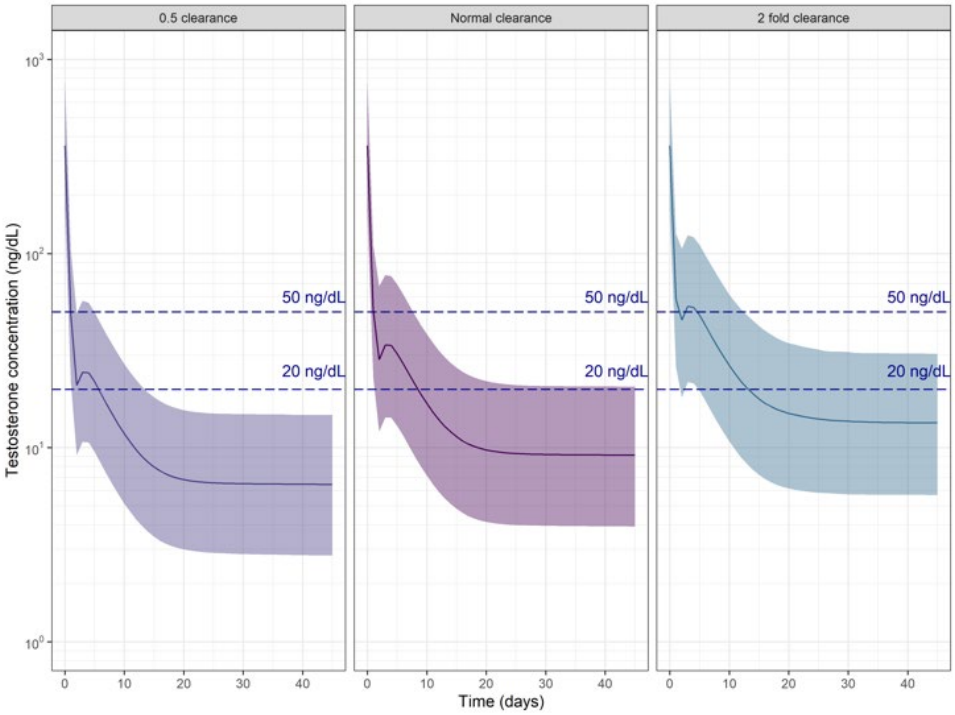
Clinically meaningful changes in drug exposure due to intrinsic or extrinsic factors observed in dedicated studies or PopPK analyses can be interpreted in context of the established comparability bounds. Specifically, clinically meaningful changes in drug exposure are to be interpreted based on the 90% CI for the GMR (test/reference) for exposure-related PK parameters (AUC, C_{max}, C_{trough}) relative to the defined lower and upper comparability bounds.

A lower comparability bound for relugolix of 0.5000 is proposed, based on the PopPK/PD analysis. In order to define a lower comparability bound as acceptance criterion for interpretation of clinically meaningful decreases in relugolix exposure, the PopPK/PD model was used to perform simulations in which the total clearance of relugolix was doubled (2-fold increase in clearance relative to the

estimated clearance from the model). The model-based simulations suggest that with a 2-fold clearance, which results in a 50% reduction in relugolix plasma concentrations, more than 90% of the patients maintain testosterone concentrations at castrate levels (< 1.73 nmol/L [< 50 ng/dL]), with a lower proportion of patients with median testosterone concentrations at profound castrate levels (< 0.69 nmol/L [< 20 ng/mL]) (

Figure 10).

Figure 10. Simulated Testosterone Concentrations upon Relugolix 120 mg Once Daily, Dosing Following a Loading Dose of Relugolix 360 mg on the First Day with Changes in Relugolix Clearance (DDI Risk)



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 (< 1.73 nmol/L) and < 20 ng/dL (< 0.69 nmol/L) 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.

An upper comparability bound of 1.5000 bound is proposed, based on the safety data from the relugolix development program at doses and exposures higher than the recommended dosing regimen of a loading dose of 360 mg on the first day followed by a 120-mg dose taken once daily, including:

- The safety profile of relugolix after administration of single doses up to 360 mg in healthy men and women in the single and multiple rising-dose study (C27001) and the thorough QT/QTc study (TAK-385-106);
- The safety profile of relugolix after administration of multiple doses of 160-mg once daily for 28 days and 180-mg doses once daily for 14 days in healthy men (C27001).

Secondary pharmacology

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 therapeutic (60 mg) dose and a supratherapeutic (360-mg) dose of relugolix on QT interval prolongation in healthy adult men and women. A total of 280 male and female participants, 18 to 55 years of age, inclusive, were enrolled and 280 participants completed the study, which was conducted in the United States.

Participants received placebo on Day 1 and were randomized (1:1:1:1 ratio) to receive 1 of 4 treatments: a single 60-mg dose of relugolix, a single 360-mg dose of relugolix, placebo, or a single 400-mg dose of moxifloxacin on Day 2. Relugolix and placebo were administered double-blind and moxifloxacin was administered open-label (after an overnight fast of at least 10 hours and continuing to fast for 4 hours post-dose). Blood samples for the determination of relugolix and moxifloxacin plasma concentrations were collected pre-dose and at prespecified time points up to 23.5 hours post-dose. Continuous Holter ECGs (12-lead) for QT interval analysis was performed and data extracted (in triplicate) at baseline on Day 1, pre-dose and at prespecified time points up to 23.5 hours post-dose on Day 2. Safety was assessed throughout the study by repeated clinical and laboratory evaluations including physical examinations, clinical laboratory tests, vital sign measurements, ECGs (12-lead) and monitoring of adverse events.

In this study, a 60-mg dose of relugolix was used as a single dose to accommodate accumulation in plasma drug concentrations after administration of a 40-mg dose once daily, the therapeutic dose and regimen anticipated as the clinical dose for women's health indications. The 360-mg dose of relugolix was selected as the supratherapeutic dose, nine times the anticipated clinical dose for women's health indications.

Pharmacodynamics

Administration of single 60- or 360-mg doses of relugolix did not prolong the QT interval/corrected QT interval (QT/QTc) interval (based on the QT interval with Bazett, Fridericia, or individual correction methods, in accordance with the ICH E14 guidance). This finding was evidenced by an upper bound of the 95% CI for the largest time-matched mean difference in QTc between relugolix and placebo (baseline-adjusted) being < 10 msec.

Table 8. QTcF for a Single 60-mg or 360-mg Dose of Relugolix vs. Placebo in Healthy Adult Men and Women (TAK 385_106)

	60-mg Relugolix vs. Placebo			360-mg Relugolix vs. Placebo		
ECG Parameter	Time at Maximum Upper Bound (hr)[a]	LS Means of Difference (msec)	Upper Bound of 95% 1-Sided CI[b]	Time at Maximum Upper Bound (hr)[a]	LS Means of Difference (msec)	Upper Bound of 95% 1-Sided CI[b]
QTcF	10	2.3051	4.0328	10	3.1059	4.8340

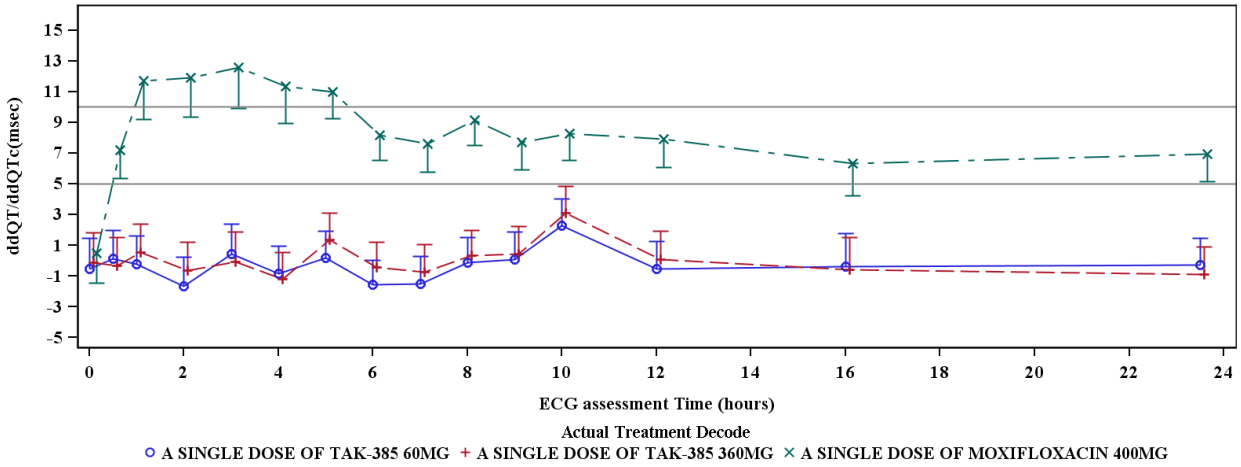
Abbreviations: CI = confidence interval; CSR = clinical study report; ECG = electrocardiogram; LS = least squares; QTcF = QT interval with Fridericia correction method.
Note: A linear mixed-effect model with repeated measures was used. Baseline, gender, treatment, scheduled time point, and interaction between treatment and scheduled time point are fixed factors in the model. Mean QTc on Day 1 was used as Baseline; unstructured was used as the covariance structure.

a. Time at the maximum of the upper bound of the 95% 1-sided CI over all time points.
b. The 95% 1-sided CI is for the difference from placebo in the LS means of the change from baseline.

Furthermore, a linear mixed-effects analysis of the change from baseline in QT/QTc intervals versus plasma concentrations of relugolix indicated that there was no concentration-related effect of relugolix on QTc prolongation, with a slope of concentration versus QT interval with Fridericia correction method

(QTcF) of -0.004 msec/ng/mL (90% CI: -0.008, 0.001). The positive control moxifloxacin resulted in the expected increase in QTcF (lower bound of placebo and baseline adjusted change in QTc > 5 msec 1 to 4 hours post-dose). The mean C_{max} after administration of single 360-mg dose of relugolix (252.94 ng/mL) was 13.8 times greater than the mean C_{max} associated with a 40-mg dose at steady state (18.31 ng/mL; MVT-601-039).

Figure 11. Least Squares Means (95% CI) ddQT/ddQTc vs. ECG Assessment Time by Treatment for QTcF in Healthy Adult Men and Women (TAK-385_106)



Abbreviations: CI = confidence interval; CSR = clinical study report; ddQT = double delta QT; ddQTc = double delta QTc; ECG = electrocardiogram; QTcF = QT interval with Fridericia correction method.

Safety Summary

In this study, a single 60-mg or 360-mg dose of relugolix was generally safe and well tolerated. All reported adverse events were mild or moderate in severity and transient in nature.

All point estimates for the ddQTcF interval were below 5 msec and the upper bound of the 90% CI was below 10 msec at each post-dose time point. Adequate assay sensitivity was demonstrated by the mixed-effects model for the double delta QT interval with Fridericia correction method (ddQTcF) interval for the moxifloxacin treatment, as the lower bounds of the 90% CI of the mean ddQTcF interval exceeded 5 msec at all post-dose time points.

The mean C_{max} after administration of single 360-mg dose of relugolix (252.94 ng/mL) was 13.8 times greater than the mean C_{max} associated with a 40-mg dose at steady state (18.31 ng/mL; MVT-601-039).

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Overall, the pharmacokinetics of the 120 mg dose of relugolix in men with prostate cancer can be considered sufficiently characterised. After oral administration of a single 360 mg loading dose, the mean (± standard deviation [± SD]) of AUC0-24 and Cmax of relugolix were 985 (± 742) ng.hr/mL and 215 (± 184) ng/mL, respectively. After administration of a 120 mg dose once daily, the mean (± SD), Cmax, Cavg (average plasma concentration over the 24-hour dosing interval), and Ctrough of relugolix at steady-state were 70 (± 65) ng/mL, 17.0 (± 7) ng/mL and 10.7 (± 4) ng/mL, respectively. The accumulation of exposure to relugolix upon once daily administration of a 120 mg dose of relugolix

is approximately 2 fold. After once daily administration of relugolix following a 360 mg loading dose on the first day of administration, steady state of relugolix is achieved by day 7.

The pharmacokinetic performance of the three tablet formulations, in terms of the total exposure (AUC), C_{max}, and time to C_{max} (t_{max}), was relatively comparable as the point estimates for C_{max} and AUC were within range of 0.80-1.25 for the comparison of the T4B (single 120 mg) and T2 (80 mg + 40 mg) tablets. The T3 tablet is expected to be comparable, because the formulation is not different from the T2 tablets aside from the film-coating. It can be concluded that the results from the clinical studies with the T2 and T3 tablet formulations can be generalized to the final market formulation and results from the various PK studies across this application can be used interchangeably.

For the interpretation of clinically meaningful changes in drug exposure due to intrinsic/extrinsic factors, comparability bounds in total exposure (AUC) of 0.5000– 1.5000 are proposed. In this context it is acceptable that Orgovyx can be administered without regards to food. It would have been preferred if the pivotal phase 3 study in men with advanced prostate cancer (MVT-601-3201) had been conducted under the same conditions as the proposed labelling posology (no food restrictions). However, this issue is not pursued, since the food effect with a decrease in exposure of relugolix is not clinically meaningful.

Given the effects of the drug-drug interaction study with voriconazole, with a 50% increase in relugolix exposure at the 40 mg relugolix dose, CYP3A4 is estimated to contribute 34% of the elimination of relugolix. The contribution of CYP3A4 to the metabolism of a relugolix dose of 120 mg is likely smaller, since an increase of 10% was observed after inhibition of CYP3A4 for this dose. Based on in vitro data, CYP2C8 is likely to be involved, but to lesser extent than CYP3A4.

Based on the many minor peaks observed in the radio-chromatograms, multiple other enzymes are likely to be involved, although not identified. Based on hydrophilic metabolites excreted in bile in rats, and hydrophilic metabolite observed in excreta in humans, UGT involvement cannot be excluded and this might be in line with the reasonably high first-pass metabolism and potential elimination via bile. In the end, the data were considered sufficient to characterize the primary/major routes of relugolix metabolism (i.e. CYP3A and intestinal microflora) and the potential impact with respect to clinically meaningful drug-drug interactions.

The expression of BCRP in the Caco-2 cells in the Applicant's study is not entirely clear and it cannot be concluded with certainty that relugolix is not a substrate for BCRP. Nevertheless, it is clear from the in vitro and in vivo studies that the absorption of relugolix is mainly affected by P-gp.

It seems unlikely that OCT1 plays a major role in the uptake of relugolix in the liver, based on the moderate passive permeability of relugolix, the high molecular weight, and wide tissue distribution observed in pre-clinical species including high tissue distribution in pituitary, which does not rely on OCT1. Although it cannot be excluded that relugolix might be a substrate for OCT1, the clinical relevance seems limited.

The greater than dose-proportional increase in exposure to relugolix is primarily attributable to dose-related saturation of intestinal P-gp (which is considered to govern oral bioavailability of relugolix), rather than systemic metabolism and/or elimination.

After administration of 80-mg doses of relugolix once daily for 14 days, the mean $t_{1/2,\ eff}$ was 25 hours, indicating that the systemic exposure (in terms of AUC) to relugolix reduced by half in approximately 24 hours and thereby supporting once daily administration.

The available data do not allow an easy comparison of the PK exposure parameters between healthy men and men with prostate cancer, as the groups are very small (n=3) and the inherent variability is large.

The central volume of distribution in the population PK model showed a trend of lower values in healthy adult men versus adult men with prostate cancer, but this trend was not statistically significant nor clinically meaningful, also taking into account the large value for apparent volume of distribution at steady state of approximately 3900 L.

Exposure to relugolix slightly increases with age in men with prostate cancer, however this is not clinically relevant and requires no dose adjustment.

A demographic summary of the Black/African American men versus the non-Black/African American men in study MVT-601-3201 showed that the distribution of body weight was similar between the Black/African American men and the non-Black/African American men in study MVT-601-3201, whereas the age of the Black/African American men was on average 6.5 years younger than the age of the non-Black/African American men in study MVT-601-3201. However, age is known to be inversely related to CL/F of relugolix, which would have been associated with a lower rather than a higher exposure to relugolix in the Black/African American men. Therefore, the higher exposure to relugolix in the Black/African American is apparently not attributable to either the body weight or age distribution.

Thus, no apparent explanation is found for the difference in exposure to relugolix between Black/African American men and non-Black/African American men. As no apparent major differences were observed in safety profile between both-sub-populations, it is agreed that the relatively modest increase in exposure to relugolix in the Black/African American men is not clinically meaningful.

As the terminal t1/2 is not affected in the subjects with renal impairment and because only 19% of the absorbed relugolix is excreted via the renal pathway, this increase in exposure may be related to an increase in oral absorption rather than a decrease in renal elimination. However, this is not completely clear.

However, in the phase 3 study not enough patients with severe renal impairment were included to draw firm conclusions on the effect of severe renal impairment (and besides the PopPK model apparently did not allow for simulations of $C_{max,ss}$). Therefore, based on the dedicated renal impairment studies with 40 mg relugolix, the conclusion remains that exposure to relugolix (AUC_{0-t}) increased 2.0-fold in subjects with severe renal function impairment and this conservative estimate should be extrapolated also to the 120 mg dose. Since the effect of severe renal impairment on the pharmacokinetics of relugolix does not fall within the comparability bounds of 0.5000 to 1.5000, this effect is reflected in section 4.4 of the SmPC where it states that as a lower dose of relugolix is not available, caution in patients with severe renal impairment is warranted upon administration of a 120 mg dose of relugolix once daily, and the amount of relugolix removed by haemodialysis is unknown.

Based on the from the hepatic impairment study with 40 mg of relugolix, no dose adjustment in mild or moderate hepatic impairment for relugolix would be required. Since hepatic impairment does not seem to play a major role in the total exposure to relugolix and it is not very likely that hepatic impairment may affect amount and saturation of (intestinal) P-gp, these conclusions may be extrapolated to the 120 mg dose. The effects of severe hepatic impairment on the pharmacokinetics of relugolix have not been evaluated. This has been reflected in section 4.4 of the SmPC.

In general, the designs of the clinical DDI studies were considered acceptable. Some of the DDI studies were done with a 40 mg dose of relugolix, where it may be noted that results from study MVT-601-054 indicate that this 40 mg dose is the dose for which the most pronounced interaction is expected (as compared to the 120 mg dose).

Effects of erythromycin on the pharmacokinetics of relugolix could be multifactorial such as inhibition of intestinal and hepatic transporters and enzymes but also affecting the intestinal flora and thereby reducing the formation of metabolite C. It was shown that the formation of metabolite C could be inhibited by erythromycin but the effect of erythromycin on relugolix exposure was very fast, while

formation of metabolite C is likely to occur later, further down the intestinal tract. Thus, the effect of erythromycin is probably related to a first-pass effect on the oral bioavailability of relugolix, as concluded in the Ryeqo assessment. The results indicate that the increase in exposure associated with co-administration of erythromycin was primarily a P-gp-mediated effect and likely to result from an increase in oral bioavailability due to inhibition of intestinal P-gp efflux. Based on these results the following text is reflected in section 4.5 of the SmPC:

P-gp inhibitors

Avoid co-administration of Orgovyx and oral P-gp inhibitors. If co-administration with once or twice daily oral P-gp *inhibitors cannot be avoided, take Orgovyx first, separate dosing by at least 6 hours, and monitor patients more frequently for adverse reactions.*

It is agreed that co-administration with oral P-gp inhibitors should be avoided. The dose separation strategy with P-gp inhibitors is already agreed upon for the Ryeqo application with the 40 mg relugolix dose. A clinical study (MVT-601-055) investigating this dose separation strategy both for the 40 mg and 120 mg relugolix dose is planned.

It is agreed that the effects of mild, moderate or strong CYP3A inhibitors will remain below the upper limit of the proposed acceptability (comparability) bounds of 0.500-1.5000 for concluding no clinically relevant effect.

Furthermore, the following is proposed in Section 4.5 of the SmPC about strong P-gp/CYP3A inducers:

Combined P-gp and strong CYP3A inducers

Avoid co-administration of Orgovyx with combined P-gp and strong CYP3A inducers. Upon co-administration with rifampicin, a P-gp and strong CYP3A inducer, the AUC and C_{max} of relugolix were decreased by 55% and 23%, respectively, due to induction of intestinal P-gp (and CYP3A) by rifampicin, which resulted in a decrease in the oral bioavailability of relugolix. Co-administration of Orgovyx with other combined P-gp and strong CYP3A inducers also may decrease the AUC and C_{max} of relugolix and may therefore reduce the therapeutic effects of Orgovyx. If co-administration cannot be avoided, increase the Orgovyx dose (see section 4.2). After discontinuation of the combined P-gp and strong CYP3A inducer, resume the recommended dose of Orgovyx once daily.

The recommendation that the Orgovyx dose should be doubled to 240 mg daily when co-administered with combined P-gp and strong CYP3A inducers is based on the results of study MVT-601-1004 which demonstrated a 2.2-fold decrease in exposure when 40 mg relugolix is co-administered with rifampin.

Based on results from the midazolam interaction study, relugolix is considered to be a weak inducer of CYP3A4. Because the relatively small decreases in exposure to midazolam observed upon co-administration with relugolix, a clinically meaningful decrease in exposure for other CYP3A4 substrates is unlikely.

The decreases in exposure to rosuvastatin upon co-administration with relugolix were unexpected considering that inhibition of the BCRP efflux transporter would be expected to result in an increase, rather than a decrease, in exposure. One might speculate that relugolix induces expression of either BCRP or OATP1B1, for which rosuvastatin is a substrate. Although the effect is not well understood, the decreases in rosuvastatin exposure for both doses (40 and 120 mg relugolix) are considered small and not clinically relevant. Relugolix does not appear to be an inhibitor of BCRP in vivo.

Rosuvastatin is also a substrate of OATP2B1, which has not been tested yet in vitro. It is known that inhibition of the intestinal OATP2B1 transporter can result in a decrease of rosuvastatin exposure. Therefore, the Applicant will investigate if relugolix is an inhibitor of intestinal OATP2B1 and submit the results of this study as a Post-Approval Measure.

Overall, from study MVT-601-3201, it can be concluded that limited data (n=20) from a Phase III trial indicate that when enzalutamide (strong CYP3A inducer and androgen receptor signalling inhibitor) is added to relugolix treatment, relugolix trough concentrations were not decreased and the same relugolix dose may be maintained. The testosterone trough concentrations were not further decreased upon co-administration with enzalutamide.

Although no dedicated studies were conducted, relugolix may be administered with acid-reducing agents, because no clinically meaningful interaction was observed based on castrate levels in patients receiving these drugs concomitantly in the Phase 3 study.

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 decrease in systemic testosterone concentrations.

The single- and multiple-rising dose study

The single- and multiple-rising dose study (**C27001**) in 176 healthy adult men in the UK with high doses (up to 180 and 360-mg dose of relugolix), showed that relugolix caused an immediate and effective suppression of gonadotropins (LH, FSH) and testosterone over 14 days. This study was performed to support the possible indication for advanced prostate cancer.

Pharmacodynamic assessments of relugolix single and multiple dose over 14-28 days demonstrated sustained testosterone suppression from 80 mg once daily, which is accompanied by strong suppression of LH. The 60 mg had variable results, while the 20 mg and 40 mg appeared ineffective in maintenance over longer time, despite the use of a 320-360 mg loading dose. These results sufficiently support the 80 mg dose for further assessment in phase 2, and employment of a loading dose in case a more rapid reduction in testosterone is needed.

Regarding safety, relugolix was well tolerated. However, in two patients reversible transaminase elevations (ALT and AST) of ≥ 3 × ULN were reported, which led to discontinuation.

MVT-601-3201

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, FSH.

Dedicated thorough QTc study

In a randomized, double-blind, placebo- and positive-controlled (open-label moxifloxacin), parallel-group, single-dose thorough QT/QTc study (**TAK-385_106)**, neither a 60-mg dose (therapeutic dose; estimated to have similar exposure as a single dose to those associated with a once daily 40-mg dose) nor a 360-mg dose (supratherapeutic dose) of relugolix resulted in prolongation of the QT interval with Fridericia's correction (QTcF) of clinical or regulatory concern. There appears some hysteresis as the largest effect was observed after 10 hours instead of around tmax (3 hours), however, with no suggestion for QT prolongation this is not considered of such relevance to be further pursued. 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. Single 60- or 360-mg doses of relugolix were generally safe and well tolerated in healthy adult men and women.

Pharmacodynamic interactions

For typical co-medication in this indication, it is noted that abiraterone is an androgen biosynthesis inhibitor that (by itself) will thus decrease testosterone concentrations. The androgen receptor (signalling) inhibitors enzalutamide and apalutamide are not expected to have any relevant effect on testosterone concentrations (by themselves), but they do exert an anti-androgenic effect. For the taxane docetaxel, any potential for PD interaction is not expected, based on its antineoplastic/cytotoxic mechanism of action.

The Applicant is currently performing an on-going phase 1 safety and tolerability study (MVT-601-049; NCT04666129) investigating the combination of relugolix with either abiraterone/prednisone, apalutamide, or docetaxel with respect to PK and PD. The clinical study report will be submitted as a Post-Approval Measure (REC). For conclusions regarding enzalutamide (strong CYP3A inhibitor and androgen receptor signalling inhibitor), see relevant section.

Pharmacokinetics/Pharmacodynamics

The relationship between testosterone concentrations and relugolix C_{trough} supports that the mean relugolix C_{trough} of 9.68 ng/mL upon once daily 120-mg dosing is strongly associated with testosterone concentrations at castrate levels (< 50 ng/dL) and profound castrate levels (< 20 ng/dL).

For the interpretation of clinically meaningful changes in drug exposure due to intrinsic or extrinsic factors observed in dedicated studies or PopPK analyses comparability bounds in total exposure (AUC) of 0.5000 – 1.5000 are proposed. The lower limit of 0.50 mirrors a 50% reduction in relugolix plasma concentrations, while more than 90% of the patients maintain testosterone concentrations at castrate levels (< 50 ng/dL).

The upper limit is based on the safety profiles of relugolix after administration of single doses up to 360 mg in healthy men and women in the single and multiple rising-dose study (C27001) and the thorough QT/QTc study (TAK-385-106), and after administration of multiple doses of 160-mg once daily for 28 days and 180-mg doses once daily for 14 days in healthy men (C27001).

There are on-going studies for which the Applicant is recommended to submit the study reports as Post-Approval Measure:

1. Final clinical study report of study MVT-601-049 in 4Q of 2023, which is an ongoing phase 1 safety and tolerability for the combination of relugolix with either abiraterone, apalutamide, or docetaxel with respect to PK and PD;
2. Final bioanalytical report for all testosterone concentration data measured at Covance Shanghai for study MVT-601-3201 as soon as the report becomes available. The expected timing of the final bioanalytical report is Q2 of 2022;
3. The clinical conduct of the dose separation and drug interaction study with an oral P-gp inhibitor (azithromycin) has been completed with FPFV occurring on 13 Aug 2021 and LPLV on 04 Oct 2021. Top-line results are expected to become available in March 2022. The Applicant is recommended to provide the CSR as a PAM as soon the final CSR becomes available. The expected timing of the final CSR is Q2 of 2022;
4. The clinical drug interaction study with the P-gp substrate dabigatran etexilate (MVT-601-057) has been initiated. The Applicant is recommended to provide the CSR as a PAM as soon as the final CSR becomes available. However, top-line results from Part 2 of the study are pending and if a clinically meaningful effect of relugolix 120 mg on the pharmacokinetics of total dabigatran is not identified, Part 1 of the study will not be conducted, and the CSR will be prepared and finalized with Part 2 results only. In this case, the final CSR is expected to become available in Q2 of 2022.

If Part 1 of the study is required, this part of the study would be initiated no later than Q3 of 2022, with the CSR available in Q4 of 2022.

5. The Applicant is recommended to investigate relugolix as a potential inhibitor of OATP2B1 in an in vitro assay with completion by Q4 of 2022.

2.6.4. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of the 120 mg dose of relugolix in men with prostate cancer can be considered sufficiently characterised. All relevant information has been reflected in the SmPC. A set of recommendations for Post-Approval Measures have been described above.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

The primary efficacy objective of the prostate cancer clinical development program was to evaluate the ability of relugolix to suppress and maintain serum testosterone to castrate levels (< 50 ng/dL) in patients with advanced prostate cancer. An overview of the clinical efficacy studies of relugolix in the treatment of prostate cancer is provided in Table 2 at the beginning of the Clinical section.

The dose of relugolix used in the main study was selected based on results from these phase 1 and phase 2 studies, and quantitative assessment of the exposure-response relationship observed for the effect of relugolix on testosterone suppression in patients with prostate cancer (see previous section). On the basis of these analyses, a single oral loading dose of 360 mg (a multiple of the maintenance daily dose) on Day 1 was selected to achieve plasma concentrations close to steady state within the first few days following the first dose. The maintenance dose of 120 mg daily was identified to ensure that > 90% of patients would achieve and maintain medical castration through 48 weeks of continuous treatment with relugolix, while maintaining an acceptable clinical safety profile.

2.6.5.2. Main study(ies)

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

The pivotal phase 3 study **MVT-601-3201** (HERO; EudraCT Number: 2017-000160-15; NCT03085095; Shore et al. N Engl J Med. 2020) aimed to evaluate the safety and efficacy of oral relugolix vs leuprolide in patients with androgen sensitive advanced prostate cancer who required at least 1 year of continuous ADT.

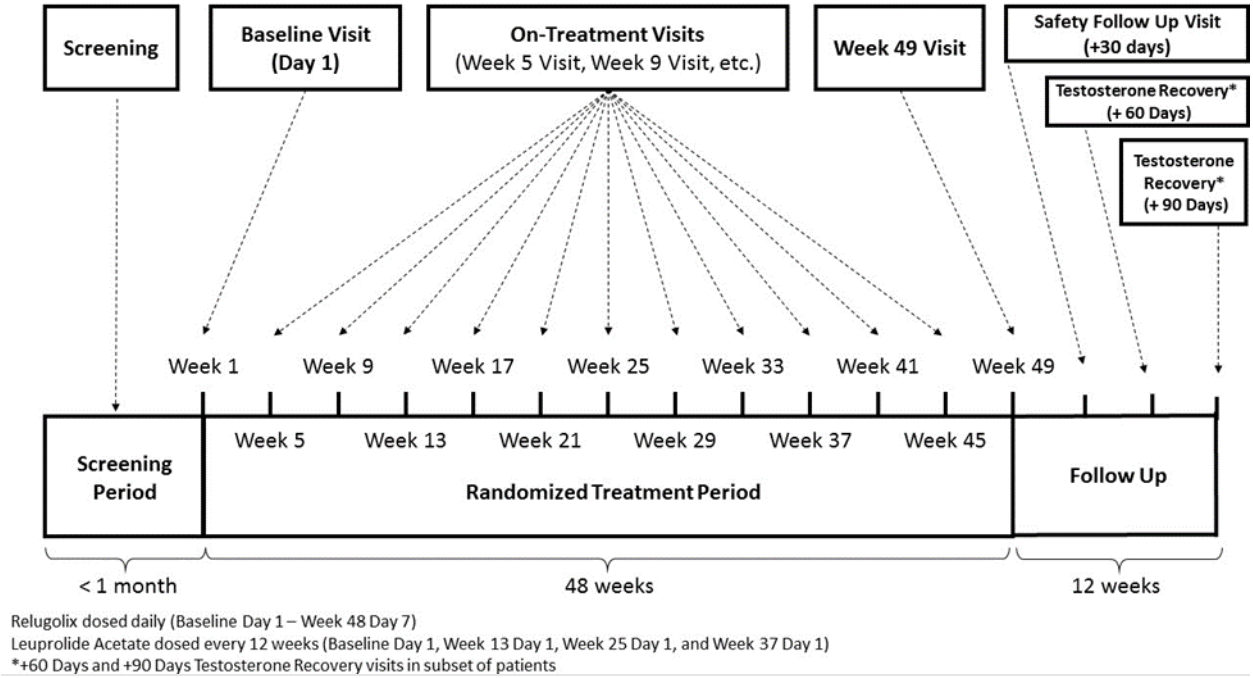
A total of approximately 1100 patients across three cohorts were to be enrolled including approximately 915 patients for the primary analysis (Cohort 1) and 390 patients with metastatic advanced prostate cancer (Cohort 2) and 138 Chinese patients (Cohort 3).

At the time of the primary analysis, the study had been performed at 155 centres globally, including North and South America, Europe, and Asia between 18-Apr-2017 (first patient randomized and dosed) and 25-Oct-2019 (last patient completed). The database lock date for the primary analysis was 10-Dec-2019. The final version of the study protocol, i.e. following Amendment 3, was 23-Oct-2018.

Methods

The study consisted 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. A schematic of the overall study design is provided in Figure 12

Figure 12. Schematic of Design Study MVT-601-3201



Study Participants

The study population consisted of **males aged ≥ 18 years old with androgen-sensitive advanced prostate cancer who**, in the opinion of the investigator, **required at least 1 year of continuous ADT for the management of the disease** and who were not candidates for surgical or radiation therapy with curative intent. Further detail regarding the eligibility criteria is provided below.

Key inclusion criteria:

A patient was eligible for inclusion in this study, if this patient:

- Was a male aged ≥ 18 years old with a histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate;
- Was a candidate for, in the opinion of the investigator, at least 1 year of continuous ADT for the management of androgen-sensitive advanced prostate cancer with one of the following clinical disease state presentations:
    - Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, such as surgery, radiation therapy, cryotherapy, or high-frequency ultrasound and not a candidate for salvage treatment by surgery; or
    - Newly diagnosed androgen-sensitive metastatic disease; or
    - Advanced localized disease unlikely to be cured by local primary intervention with either surgery or radiation with curative intent;

Note: Once 915 patients were enrolled worldwide, only patients with metastatic advanced prostate cancer were eligible for the study in all regions, except China, where both metastatic and non-metastatic patients continued to be enrolled.

- Had a serum PSA concentration at the screening visit of > 2.0 ng/mL, or, when applicable, post radical prostatectomy of > 0.2 ng/mL, or post radiation therapy, cryotherapy, or high frequency ultrasound > 2.0 ng/mL above the post interventional nadir;
- Had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Key exclusion criteria:

A patient was not eligible for inclusion in this study, if this patient:

- In the investigator's opinion, was likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating ADT;
- Previously received GnRH analog or other form of ADT (oestrogen or antiandrogen) for > 18 months total duration. If ADT was received for ≤ 18 months total duration, then that therapy must have been completed at least 3 months prior to baseline;
- Previous systemic cytotoxic treatment for prostate cancer (e.g., taxane-based regimen);
- Metastases to brain per prior clinical evaluation;
- History of surgical castration;
- Had abnormal laboratory values at the screening visit that suggested a clinically unstable underlying disease;
- Had haemoglobin A1c (HbA1c) > 10% in patients previously diagnosed with diabetes mellitus. HbA1c > 8% in patients whose diabetes mellitus was previously undiagnosed;
- Had jaundice or known current active liver disease from any cause;
- Had a history of any of the following within 6 months before baseline Day 1: myocardial infarction; unstable angina; unstable symptomatic ischemic heart disease; New York Heart Association class III or IV heart failure; thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events); or any other significant cardiac condition (e.g., pericardial effusion, restrictive cardiomyopathy, severe untreated valvular stenosis, or severe congenital heart disease);
- Had any ECG abnormalities (see Clinical AR for details);
- Had uncontrolled hypertension despite appropriate medical therapy, had hypotension, or had bradycardia;
- Had received previous treatment with relugolix in a clinical study;
- Had a history of gastrointestinal disease or procedure that could interfere with the oral absorption or tolerance of relugolix;

Treatments

Patients were randomized 1:1 to receive one of the following study drugs:

- Relugolix 360 mg (3 × 120 mg tablets) single oral loading dose on Day 1 followed by one 120 mg tablet orally once daily for 48 weeks;

- Leuprolide 3-month depot injection, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) every 12 weeks for 48 weeks (last injection occurred 12 weeks prior to the end of the treatment period).

Patients randomized to relugolix received the first oral (loading) dose on Day 1 in the clinic.

Leuprolide was administered on Day 1 at the clinic and thereafter at 12-week intervals, either by intramuscular or subcutaneous injection; investigators were instructed to follow product instructions provided by the manufacturer. Administration of an antiandrogen (e.g. bicalutamide, flutamide, nilutamide) was permitted for the first 4 weeks or longer if indicated, as determined by the investigator, for the management of the initial flare response. The dose of leuprolide 3-month depot injection was selected as per product instructions provided by the manufacturer for both the 22.5 mg and the 11.25 mg dose.

Dose modifications

Dose modifications were not permitted during the study.

Prohibited medications

The following systemic medications were prohibited prior to the first dose of study medication until the End of Treatment visit and the Follow-up Period was complete, e.g.: GnRH analogues; GnRH receptor antagonists; antiandrogens; CYP17 inhibitors; other androgen suppressing agents or androgens; 5alpha reductase inhibitors; Class IA and III antiarrhythmics; moderate and strong CYP3A and P -glycoprotein inducers; moderate/strong P-glycoprotein inhibitors; high-dose biotin supplements; herbal therapies.

Objectives and outcomes/endpoints

The **objectives and outcomes/endpoints** of the study are listed in Table 9.

For the primary efficacy endpoint, there were two evaluation criteria in the protocol to support different regulatory requirements for assessing benefit, see Table 9. Evaluation Criterion 1 was a regulatory requirement from the FDA and was the trial success criterion for the primary efficacy endpoint. Evaluation Criterion 2, the primary efficacy endpoint required by EMA, was the first to be tested in the order of ranked key secondary endpoints to assess non-inferiority of relugolix compared with leuprolide after Evaluation Criterion 1 was passed (see ***Statistical methods***).

The **primary hypotheses** associated with these 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 through Week 49 Day 1 is ≥ 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 non-inferiority margin of –10%.

  Null hypothesis H_{02}: $\pi_R - \pi_L < -10\%$ versus Alternative hypothesis H_{a2}: $\pi_R - \pi_L \geq -10\%$

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

The -10% non-inferiority margin for the comparison of relugolix versus leuprolide was based on regulatory precedence of the pivotal assessment of the GnRH receptor antagonist degarelix versus leuprolide as well as studies of branded GnRH receptor agonist generics.

Table 9. Study MVT-601-3201 Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary Efficacy	
To evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels of < 50 ng/dL (1.7 nmol/L) in men with androgen sensitive advanced prostate cancer	The **primary endpoint** is the **sustained castration rate**, defined as the cumulative probability of testosterone suppression to < 50 ng/dL while on study drug from Week 5 Day 1 (Day 29) through Week 49 Day 1 (Day 337). • Evaluation Criterion 1: to determine whether the sustained castration rate (defined as the cumulative probability of testosterone suppression to < 50 ng/dL while on study drug from Week 5 Day 1 through Week 49 Day 1) for relugolix is ≥ 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group was calculated and must be at least 90% for this criterion to be met. • Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide every 3-month depot injection as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the two treatment groups was calculated and must be greater than or equal to the non-inferiority margin of -10% for this criterion to be met.
Key Secondary Efficacy (Alpha-Protected for Hierarchical Hypothesis Testing)	
To determine the time course and change in serum testosterone	Cumulative probability of **testosterone suppression** to < 50 ng/dL prior to dosing **on Week 1 Day 4**.
	Cumulative probability of **testosterone suppression** to < 50 ng/dL prior to dosing **on Week 3 Day 1**.
To evaluate the time course and magnitude of PSA reduction	Proportion of patients with **PSA response** (by Prostate Cancer Clinical Trials Working Group 3 [Scher et al. 2016]) at Week 3 Day 1 followed with the confirmation at Week 5 Day 1.
To determine the time course and change in serum testosterone	**Profound castration rate** defined as cumulative probability of testosterone suppression to < 20 ng/dL (0.7 nmol/L) prior to dosing on Week 3 Day 1.
To evaluate the effect of relugolix and leuprolide on endocrine pharmacodynamic parameters.	**FSH level** at Week 25 Day 1.
To describe the time course and magnitude of development of castration-resistant prostate cancer [a]	**Castration resistance-free survival** during the 48-week treatment in patients with or without metastatic prostate cancer (not analysed for the primary analyses).
To evaluate testosterone recovery following discontinuation of study drug	Cumulative probability of **testosterone recovery** to > 280 ng/dL at the 90-day follow-up in approximately 150 patients who complete 48 weeks of treatment and who do not plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of leuprolide 3-month depot).
Other Secondary Efficacy (Not for Hierarchical Hypothesis Testing)	

Objective(s)	Endpoint(s)
To determine the time course and change in serum testosterone	Sustained profound castration rate from Week 5 Day 1 through Week 49 Day 1 defined as the cumulative probability of testosterone suppression to < 20 ng/dL while on treatment from Week 5 Day 1 through Week 49 Day 1; Sustained profound castration rate from Week 25 Day 1 through Week 49 Day 1 defined as the cumulative probability of testosterone suppression to < 20 ng/dL while on treatment from Week 25 Day 1 through Week 49 Day 1.
To evaluate the time course and magnitude of PSA reduction during treatment	Proportion of patients with confirmed PSA response at Week 5 Day 1; Proportion of patients with PSA concentration < 0.02 ng/mL at Week 25 visit.
To describe the time course and magnitude of PSA progression and development of castration-resistant prostate cancer during treatment	Time to PSA progression per Prostate Cancer Clinical Trials Working Group 3 (Scher et al. 2016).
To evaluate testosterone recovery following discontinuation of study drug	Cumulative probability of testosterone recovery back to ≥ 50 ng/dL or back to baseline or ≥ 280 ng/dL at the 90-day follow-up in approximately 150 patients who complete 48 weeks of treatment and who do not plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of leuprolide 3-month depot)
To evaluate the impact of treatment on **quality of life** using validated patient-report outcome instruments.	• Absolute values and changes from baseline in the scores of the EORTC-QLQ-C30 global health domain, and the EORTC-QLQ-PR25 sexual activity and hormonal-treatment-related symptom subdomains, at regular intervals during treatment, and as applicable during the Follow-up and/or End of Treatment visits; • Absolute values and changes from baseline of the remaining domains in the EORTC QLQ-C30 and EORTC QLQ-PR25, as well as the EuroQol EQ-5D-5L questionnaire, at regular intervals during treatment, and as applicable during the Follow-up visits.
Safety	
To evaluate the **safety** of relugolix 120 mg once daily in men with androgen-sensitive advanced prostate cancer.	Treatment-emergent adverse events (hereafter referred to as adverse events), clinical laboratory tests, and vital sign measurements.
Pharmacodynamics	
To evaluate the effect of relugolix and leuprolide on endocrine pharmacodynamic parameters.	Endocrine marker effects of relugolix and leuprolide as measured as absolute values and change from baseline for: • LH at the Day 4, Week 5, Week 25, and Week 49 visits; • FSH at the Day 4, Week 5, Week 25, and Week 49 visits; • Dihydrotestosterone at the Week 5, Week 25, and Week 49 visits; • Sex hormone-binding globulin at Week 5, Week 25, and Week 49 visits.
Pharmacokinetics	
To collect relugolix plasma concentration data to further evaluate relugolix population pharmacokinetics and the relationship between relugolix exposure and serum testosterone.	Pre-dose relugolix plasma concentrations. The population pharmacokinetic analysis and analysis between relugolix exposure and serum testosterone will be provided in a separate report.
To characterize the relugolix plasma pharmacokinetic parameters in subsets of patients from China and Japan.	Single- and repeat-dose plasma relugolix pharmacokinetic parameters such as C_{max}, $AUC_{0-\tau}$, and t_{max} in subsets of patients from China and Japan. The pharmacokinetics in Chinese patients will be provided in a separate report.

Objective(s)	Endpoint(s)
Exploratory	
To explore overall survival	**Overall survival** defined as time from randomization to date of death prior to data cut-off date.

Abbreviations: AUC_{0-T} = area under the curve from time 0 to tau; C_{max} = maximum plasma concentration; EuroQol EQ-5D-5L = European Quality of Life 5-Dimension 5-Level Questionnaire; FSH = follicle-stimulating hormone; LH = luteinizing hormone; PSA = prostate-specific antigen; t_{max} = time to maximum plasma concentration.

Note: Testosterone was assayed by a central bioanalytical laboratory, see below under **Efficacy analyses**.

[a] Castration resistance-free survival was not assessed in the primary analysis of the study, but is was assessed at the time of the final analysis.

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 non-inferiority margin of -10% 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 non-inferiority of relugolix to leuprolide.

In total, approximately 1100 patients across three cohorts were to be enrolled including approximately 915 patients for the primary analysis (Cohort 1, enrolled under Protocol Amendment 2; see **Conduct of study**) and 390 patients with metastatic advanced prostate cancer (Cohort 2) and 138 Chinese patients (Cohort 3, enrolled in China and Taiwan), both enrolled under Protocol Amendment 3.

Randomisation and blinding (masking)

Patients were randomized in a 2:1 ratio to either the relugolix or the leuprolide treatment group by using an interactive web response system (IWRS). Randomization was stratified by geographic region, presence of metastatic disease, and age as follows:

- Geographic region: Europe vs North and South America vs Asia and rest of world;
- Presence of metastatic disease (by locally read imaging; metastases in regional lymph node(s) are considered N1 and, therefore, stratified as non-metastatic): yes vs no; and
- Baseline age: ≤ 75 years old vs > 75 years old.

Blinding was not applicable, as this was an open-label study. Some data access restrictions intended to minimize bias were put in place. The blinded team consisted of a statistician in charge of writing the statistical analysis plan (SAP) and a programmer. The rest of the study team was unblinded, including other personnel involved in SAP development.

Statistical methods

The SAP was finalized on 12-Sep 2019 then amended on 29-Oct-2019 and 07-Nov-2019 to incorporate FDA advice, and on 13-Jul-2020 to clarify definitions of analysis populations and to clarify that pre-

specified descriptive analyses (i.e., the alpha-protected endpoints) would not be updated for the final analysis. The procedures described in the SAP supersede those described in the protocol.

There were two analyses for this study: a primary analysis and a final analysis (and thus no interim analysis). The primary analysis of safety and efficacy occurred after 934 patients were randomized to the study (Cohort 1) and completed the 48-week treatment period and 30-day safety follow-up visit or discontinued early. The final analysis of the study occurred after approximately 390 patients with metastatic disease (of whom, 295 patients were also included in the primary analysis [Cohort 1]) had been randomized to the study (Cohort 1 and Cohort 2) and had either completed 48 weeks of study treatment inclusive of the 30-day safety follow-up visit or discontinued early. Results of the efficacy analysis in the China cohort (Cohort 3) were not included in the primary analysis clinical study report (CSR) and are therefore not included in this assessment report.

All statistical analyses were conducted using SAS® Version 9.2 or higher.

A statistical test for the primary endpoint was assessed at a two-sided $\alpha = 0.05$ significance level, and all confidence intervals (CIs) were reported as two-sided, unless otherwise stated.

Where appropriate, variables were summarized descriptively by study visit. For categorical variables, the count and proportions of each possible value were tabulated by treatment group. For continuous variables, the number of patients with non-missing values, mean, median, standard deviation, minimum, and maximum values were tabulated.

Analysis populations

For the **primary analysis**, the **modified intent-to-treat** (mITT) **population** was defined as all randomized patients who received at least one dose of any study drug. Unless otherwise specified, all analyses used the mITT population by treatment group as assigned by randomization (not by actual treatment received). The mITT population is the primary population used for efficacy endpoints.

For the **final analysis**, the following populations were used for the efficacy data.

- mITT Final Analysis Population: defined as all patients randomized who had taken at least one dose of any study drug for the final analysis of the study. Only the CRFS endpoint was analysed in this population.
- mITT Metastatic Patient Population: defined as a subset of the mITT Final Analysis Population of patients who had metastatic prostate cancer. Only the CRFS endpoint was analysed in this population, at the time of final analysis of the study.

The **per-protocol population** was defined as those members of the mITT population who did not have important protocol deviations (IPDs). This population was used for sensitivity analysis of the mITT population for the primary efficacy endpoint. The per-protocol population and the associated subset of IPDs were identified prior to database lock.

The **safety population** was defined as all randomized patients who received at least one dose of study drug. Unless otherwise specified, safety data were analysed by treatment group according to the actual treatment received (not the randomized treatment). The safety population was the primary population used for safety analyses.

Efficacy analyses

Stratified analyses incorporated the randomization stratification factors geographic region, presence of metastatic disease, and baseline age. If the group of patients from any of the individual randomization stratification factors (e.g., with presence of metastatic disease) comprised < 10% of the entire mITT population, this stratification factor was collapsed for stratified analyses. In addition, if there were < 15

patients in one of the 12 strata, stratification factors of presence of metastatic disease and baseline age was used in the stratified analysis for more robust strata-adjusted estimation of treatment effect.

For efficacy endpoints related to testosterone test results, analytical testosterone results from the central bioanalytical laboratory using a liquid chromatography-tandem mass spectrometry method, with a lower limit of quantification of 5 ng/dL, were used. Unless the endpoints were related to testosterone recovery, results from safety follow-up, 60-day and 90-day testosterone recovery were excluded from the efficacy analyses.

Primary efficacy analysis

Kaplan-Meier analysis and censoring rules

In general, patients with testosterone escape (defined as any testosterone test result rising above the castrate level [≥ 50 ng/dL]) between Week 5 Day 1 through Week 49 Day 1 were considered as an event in the Kaplan-Meier analysis. The time from the date of the first dose to date of the first testosterone escape was considered as the event time. Patients who had not reached castrate level at Week 5 Day 1 were considered as having had an event at the target day of Week 5 Day 1.

Patients who discontinued from the study prior to Week 5 Day 1 will be censored at the target day of Week 5 Day 1. In addition, patients without a Week 5 Day 1 assessment will be considered to have had an event at the target day of Week 5 Day 1.

For patients reaching castrate levels at Week 5 Day 1, the following rules will be applied to the Kaplan-Meier analysis for estimation of sustained castration rate with consideration for missed visits. Time to event or censoring, whichever occurs first, will be used in Kaplan-Meier analysis.

a) Patients who had one or more consecutive missed visits (i.e., a visit gap of > 42 days) and had a non-castrate assessment immediately after the missed visit(s) will be considered as having an escape at the target day of the earliest missed visit prior to the non-castrate assessment;

b) Patients with one missed visit who has a castrate assessment immediately before and after the missed visit will be assumed to be castrated at the missed visit;

c) Patients with two or more consecutive missed visits (i.e., a visit gap of > 70 days) and who had a castrate assessment immediately before and after the missed visits will be censored at the last available testosterone assessment prior to the missed visits.

Note: A visit gap of 70 days for two missed visits was used to consider the duration between two expected visits (8 weeks), plus the visit windows allowed per protocol (7 days for each expected visit with a total of 2 weeks as visit window for two visits). A visit gap of 42 days for one missed visit was used to consider the visit of every 4 weeks, and ± 7 days as the visit window, per protocol.

Otherwise, patients will be censored at the last available assessment prior to the follow-up visits, including patients who discontinue from the trial for reasons other than a non-castrate testosterone level.

If the above censoring rules are applied to a patient in multiple instances, the date of the earliest censoring for missed visits will be used as the date of censoring.

In addition, patients who had initiated therapies known to suppress testosterone will be censored at the time of last testosterone assessment prior to the initiation of such therapies.

The time to event or censoring, whichever comes first, will be summarized by the Kaplan-Meier method. If the event time or censoring time is after Day 337, Day 337 will be used as the event time or censoring time.

Sensitivity analyses to the primary analysis

To assess the robustness of the primary analysis for Evaluation Criteria 1 and 2, the following sensitivity analyses of the primary endpoint were performed.

- ***Sensitivity Analysis 1***: Analysis of the primary endpoint was repeated under the per-protocol population.
- ***Sensitivity Analysis 2***: In addition to the censoring rules described above, patients who had received concomitant medications and herbal supplements that could possibly affect testosterone levels during study treatment were excluded from the analysis.
- ***Sensitivity Analysis 3***: Patients who had missed two or more consecutive visits after Week 5 Day 1 (above censoring rule c) or discontinued from the study early were considered to have an event at the target day of the earliest missed visit.
- ***Sensitivity Analysis 4***: In order to assess the impact of delayed testosterone suppression to castrate level, analyses of the primary endpoint were repeated by considering that patients who had not reached castrate level at Week 5 Day 1, were censored at Week 5 Day 1.

Subgroup analysis for the primary efficacy endpoint

Subgroup analyses of the primary efficacy endpoint were performed to determine whether treatment effects were consistent across clinically important subgroups. Subgroups included but were not limited to geographic region, ethnicity, presence of metastatic disease, age, race, clinical disease presentation, Gleason score, baseline testosterone, and baseline PSA levels. The odds ratio (OR) and its 95% CI based on a logistic regression model were displayed in a forest plot for each subgroup.

In addition, testosterone castration rates at Week 49 Day 1 (Day 337) for the two different dose levels (22.5 mg vs 11.25 mg) in the leuprolide group and their 95% CIs have been provided separately.

Key secondary efficacy endpoints

The primary and the key secondary efficacy analyses were performed at an overall two-sided type I error of 0.05. A test was deemed statistically significant if the two-sided p---value rounded to 4 decimal places was less than 0.05. If the result of the primary endpoint analysis met the respective evaluation criterion of the primary endpoint, the key secondary endpoints were tested with a fixed-sequence testing procedure (as illustrated in Table 10) to maintain the overall familywise error rate of 0.05 for the testing of primary and key secondary endpoints.

All p-values (if provided) aside from the endpoints listed in the testing order were not adjusted in multiplicity, thus were at a nominal level of 0.05.

Table 10. Testing Order and Timing of Analysis for Primary and Key Secondary Endpoints for Different Regulatory Agencies

	Testing Order for the FDA		Testing Order for Other Health Authorities Apart from the FDA	
Endpoints	**At Primary Analysis**	**At Final Analysis**	**At Primary Analysis**	**At Final Analysis**
Sustained castration rate per Evaluation Criterion 1 (≥ 90% in relugolix)	1	No Update	NA	No Update
Sustained castration rate per Evaluation Criterion 2 (non-inferiority of relugolix compared with leuprolide)	2	No Update	1	No Update
Castration rate on Week 1 Day 4	3	No Update	2	No Update
Castration rate on Week 3 Day 1	4	No Update	3	No Update

Endpoints	Testing Order for the FDA		Testing Order for Other Health Authorities Apart from the FDA	
	At Primary Analysis	At Final Analysis	At Primary Analysis	At Final Analysis
Confirmed PSA response rate at Week 3 Day 1	5	No Update	4	No Update
Profound castration rate at Week 3 Day 1	6	No Update	5	No Update
FSH level at Week 25 Day 1	7	No Update	6	No Update
Castration resistance-free survival during the 48-week treatment in patients with metastatic prostate cancer [a]	NA	8	NA	7
Castration resistance-free survival during the 48-week treatment in patients with or without metastatic prostate cancer [a]	NA	9	NA	8
Time to testosterone recovery back to > 280 ng/dL at the 90-day follow-up in patients participating in testosterone recovery follow-up [b]	10	NA	9	NA

Abbreviations: FDA = Food and Drug Administration; FSH = follicle-stimulating hormone; NA = not applicable; PSA = prostate-specific antigen.

[a] Castration resistance-free survival and time to testosterone recovery back to > 280 ng/dL at the 90-day follow-up were to be tested at the final analysis only if all the preceding endpoints reached statistical significance in the primary analysis. Endpoints in the higher order were not updated with descriptive statistics in the final analysis.

[b] Analysis of time to testosterone recovery was performed at the primary analysis for exploratory purposes without formal testing. Testing order of time to testosterone recovery in the final analysis was to be preceded by castration resistance-free survival; however, the testosterone recovery analysis was not formally tested at the final analysis, because the results for castration resistance-free survival did not achieve statistical superiority.

Other secondary efficacy endpoints

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. See also Table 9.

For patient reported outcomes, three questionnaires (EORTC QLQ-C30, EORTC QLQ-PR25, and EuroQoL 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. Scores and change from baseline scores from each scale were summarized using a mixed model for repeated measures (EORTC QLQ-C30 and EORTC QLQ-PR25) or descriptive statistics (EuroQoL EQ-5D-5L).

Exploratory efficacy endpoint

For overall survival, the Kaplan-Meier method was used to describe survival distributions by treatment group. Patients were censored at the last contact date prior to data cut-off date if patient was known to be alive prior to database lock date.

Changes in planned analysis

There were no changes to the planned analysis primary analysis of the study after database lock (for the primary analysis). The following additional analyses were performed after the database lock for the primary analysis. No changes were made in the planned analyses of the final analysis.

As the enrolment for the follow-up of testosterone recovery had been completed for the patients enrolled under protocol Amendment 2, an analysis of time to testosterone recovery back to > 280 ng/dL at the 90-day follow-up was performed at the primary analysis, but for exploratory purposes

without formal testing. In the final analysis testing order, time to testosterone recovery (without any updates) was to be preceded by CRFS; however, the testosterone recovery analysis was not formally tested for the final analysis. See also footnote b of Table 10.

To better understand the incidence of major adverse cardiovascular events (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.

A broad post-hoc assessment of risk factors for cardiovascular and cerebrovascular events in all patients was conducted. The assessment included: 1) life-style related risk factors (including former or current use of tobacco, heavy alcohol use and body mass index > 30), 2) any cerebrovascular or cardiovascular risk factors (including medical history terms related to peripheral arterial disease, hypertension, dyslipidaemia, diabetes, atrial fibrillation, aortic stenosis, mitral stenosis, endocarditis, mechanical valve replacement, chronic kidney disease, prior TIA, stroke or intracranial haemorrhage, prior myocardial infarction or cerebrovascular disease, chronic obstructive pulmonary disease, chronic liver disease, carotid stenosis or occlusion, venous thromboembolism, heart failure and myopathies), and 3) any history of MACE (as determined by the Myocardial Infarction standardised MedDRA query [SMQ] [broad], Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ [broad], and deaths due to all causes).

Results

Unless stated otherwise, efficacy results of the primary analysis of study MVT-601-3201 are presented here. As is shown in Table 10, only the results of the key secondary endpoint CRFS were updated at the final analysis.

Recruitment and participant flow

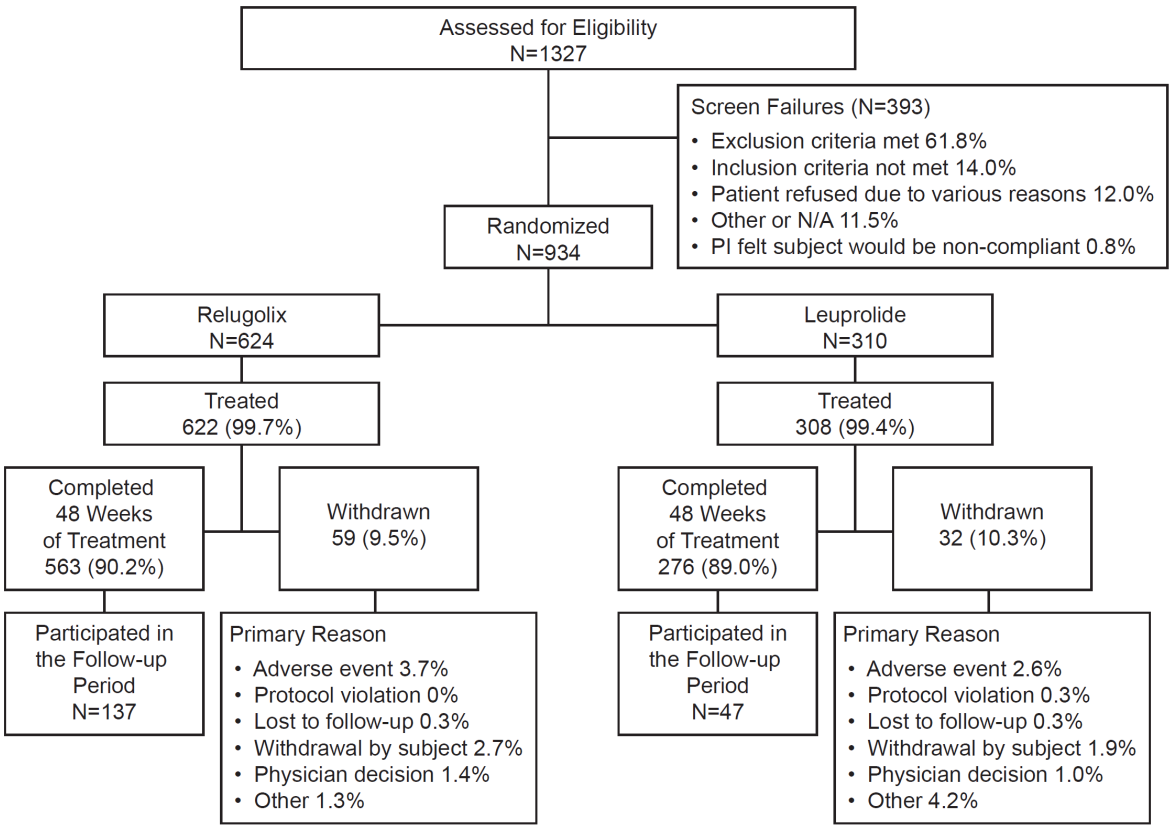
For the primary analysis, the first patient was randomized (and dosed 18-Apr-2017 and the last patient completed the study 25-Oct-2019. The database lock date for the primary analysis was 10-Dec-2019.

Patient disposition and primary reasons for early discontinuation of study drug are summarized in Figure 13.

A total of 1327 patients were screened and 934 patients were randomized at 155 centres globally, including North and South America, Europe, and Asia and rest of world as part of the primary analysis. 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). Two patients (one in each group) met exclusion criteria and were discontinued from the study. The other two patients withdrew consent before receiving study drug.

Figure 13. Disposition of Patients (Primary Analysis)



Abbreviations: N = number of patients; N/A = not applicable; PI = principal investigator.

Refer to the Clinical AR for information on recruitment and participant flow at the time of final analysis with a database lock date of 23-Sep-2020.

Protocol deviations

A summary of Important Protocol Deviations (IPDs), by category and frequency, is presented in

Table 11.

Table 11. Summary of Important Protocol Deviations (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%)

Abbreviations: 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.

Refer to the Clinical AR for further information on these IPDs.

Conduct of study

The original study protocol (dated 13-Jan-2017) 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. However, because of a typographical error in an exclusion criterion, the meaning of that criterion was inadvertently changed. This amendment was initially submitted to a regulatory authority, then withdrawn. The typographical error in the exclusion criterion was corrected and all other clarifications previously stated above were included in a new version, Amendment 2 (dated 18-Jan-2018, i.e. 16 days later than Amendment 1). To alleviate the burden of study visits on participants, this amendment also eliminated the Day 22 visit, resulting in fewer patients having data at this visit compared with the rest of the study visits. 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.

The primary purpose of Amendment 3 (dated 23-Oct-2018) was to include an additional alpha-protected key secondary endpoint of CRFS, an important indicator of disease progression, in the final analysis. To support this analysis, the protocol allowed for an additional cohort of approximately 100 patients with metastatic disease to be enrolled to ensure an appropriate level of statistical power for the analysis (targeting ~390 metastatic patients in total including those enrolled with the initial cohort of 925 patients). The choice to enrich the study with metastatic patients was due to the higher incidence of castration resistance in patients with metastatic disease. In addition, to support registration in China, a target number of 138 metastatic and nonmetastatic patients from China (enrolled in China and Taiwan) was specified, including those enrolled in Taiwan as part of the initial cohort of 915 patients.

As a result of the protocol amendments, this study has two planned analyses: the primary and the final analyses, see ***Statistical methods***.

Baseline data

Demographic characteristics

The demographic characteristics of the patients in the mITT population are presented in

Table **12**.

Table 12. Summary of Patient Demographics (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%)
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%)

Abbreviations: Max = maximum; Min = minimum; mITT = modified intent-to-treat; N = number of patients in the treatment group; SD = standard deviation.
Percentages are based on the total number of patients in the modified intent-to-treat population for each treatment group or total.

For the mITT Final Analysis Population, general baseline characteristics of patients were consistent between the treatment groups (data not shown). For the metastatic patients in the mITT final analysis population, general baseline characteristics were also similar between the treatment groups and similar with the mITT Final Analysis Population as a whole (data not shown).

Disease characteristics

Disease-specific baseline characteristics of patients in the mITT population are presented in

Table **13**.

Table 13. Summary of Disease-Specific Baseline Characteristics (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 local primary intervention with either surgery or radiation 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%)

	Relugolix (N = 622)	Leuprolide (N = 308)	Total (N = 930)
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 [c]	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%)
Had prior prostatectomy			
No	381 (61.3%)	183 (59.4%)	564 (60.6%)
Yes	241 (38.7%)	125 (40.6%)	366 (39.4%)
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

Abbreviations: ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; Max = maximum; Min = minimum; mITT = modified intent-to-treat; N = number of patients in the treatment group; PSA = prostate-stimulating hormone; SD = standard deviation.

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

[a] Disease 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.

[b] Gleason score is determined by adding primary and secondary Gleason scores together.

[c] One patient in the leuprolide group was given an ECOG score of 3 at screening due to the use of crutches as a result of a surgical vascular procedure on his leg. By baseline on Day 1, the patient no longer needed crutches and his ECOG score had improved to 0.

For the mITT Final Analysis Population, the disease-specific baseline characteristics of patients were consistent between the treatment groups. As a results of Amendment 3, the mITT Final Analysis Population was enriched for patients with metastatic disease compared to the mITT at primary analysis (data not shown). For the metastatic patients in the mITT Final Analysis Population (the mITT Metastatic Patient Population), the disease-specific baseline characteristics were also similar between the treatment groups. Overall, disease-specific baseline characteristics for metastatic patients were consistent with a high burden of disease (data not shown).

Prior and concomitant medical therapies that could alter testosterone or PSA levels

Prior and concomitant therapies for prostate cancer include ADT, therapies that could alter testosterone or PSA levels, and radiation therapy.

Prior androgen deprivation therapy

A small percentage of patients had used prior ADT (11.9%), with 13.0% in the relugolix group and 9.7% in the leuprolide group

Table **13**).

Concomitant therapies that could alter testosterone or PSA levels

Various concomitant therapies may have the potential to alter testosterone or PSA levels and therefore could have affected the interpretation of the efficacy data in this study. As such, therapies that were likely to affect analysis of efficacy were identified.

Therapies known to suppress testosterone

Therapies known to suppress testosterone were prohibited medications during the study but could be started on or after Week 49. 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. Almost all cases (14 of the 15 patients) concerned ADT given as the subsequent therapy to continue their ADT regimen, but because of variations in Week 49 Day 1 visit scheduling, these therapies were given less than 12 weeks after the last leuprolide injection on study, and were therefore, captured as concomitant medications. One patient (in the leuprolide group) received leuprolide before Week 49, which was a protocol deviation.

Antiandrogen therapies

As expected, more patients in the leuprolide group received antiandrogen therapy (allowed per the protocol) initiated during the first 4 weeks of study treatment (23.4%) than in the relugolix group (0.2%) to manage clinical flare. One patient (0.2%) in the relugolix group initiated bicalutamide therapy on Day 5, the same day that the patient withdrew and early terminated from the study.

Therapies that could possibly affect testosterone

Overall, 125 patients (13.4%) took at least one concomitant medication or herbal supplement that could possibly affect testosterone. More patients in the leuprolide group (30.5%) took at least one therapy compared with the relugolix group (5.0%). Bicalutamide (allowed per the protocol) was the most frequently used therapy in the leuprolide group (26.6%), and for the majority of patients this antiandrogen therapy was initiated in the first 4 weeks for the prevention of initial flare for 4 weeks or longer (23.1%, see above). Enzalutamide was the most frequently used therapy in the relugolix group (17 patients; 2.7%) and similarly used in the leuprolide group (6 patients; 1.9%). Megestrol, medroxyprogesterone, and cyproterone were prohibited medications on study, but were used for the treatment of hot flush and/or appetite stimulant in both groups (by less than 1% of patients). Abiraterone (four patients [1.3%] in the leuprolide group), goserelin (two patients [0.6%] in the leuprolide group), and degarelix (one patient [0.3%] in the leuprolide group) were prohibited alternative treatments for prostate cancer, and all patients who used these medications on study received IPDs and were discontinued from the study. There were two patients who used herbals containing glycyrrhiza glabra (liquorice) on study: one patient (0.2%) in the relugolix and one (0.3%) in the leuprolide group.

To assess the impact of concomitant medications and herbals that could possibly affect testosterone, a sensitivity analysis (Sensitivity Analysis 2) of the primary endpoint was performed excluding all such patients.

Therapies that could possibly affect prostate-specific antigen

All systemic therapies, except for ADT, used for the treatment of prostate cancer were included in this list. In addition to the information provided above under the previous heading, docetaxel (allowed per protocol after 2 months of study initiation) was used in similar proportions of patients in both groups (1.3% [n=8] in the relugolix group and 1.6% [n=6] in the leuprolide group).

Prior and concomitant radiation therapy

The majority of patients who received radiation therapy after study treatment initiation was in the primary setting (9.6% in the relugolix group and 12.0% in the leuprolide group, 10.4% overall). All but three patients received radiation therapy to the prostate bed after 2 months of initiating ADT, in line with the protocol. The three patients who started radiotherapy to the prostate bed (in either primary or salvage setting) less than 2 months after study initiation (all three in the relugolix group) were deemed protocol deviations. The use of radiotherapy in the palliative setting was similar across the two groups (3.9% in the relugolix group and 3.2% in the leuprolide group).

Numbers analysed

The number of patients included in each analysis set is presented in Table 14. Except for the four patients who did not receive study drug (two patients in each treatment group), all randomized patients were included in the mITT and safety primary analysis populations.

Table 14. Number of Patients in Each Analysis Population by Treatment Group (All Randomized Patients) – Primary Analysis

Patient Population	Relugolix (N = 624)	Leuprolide (N = 310)	Total (N = 934)
mITT Population	622 (99.7%)	308 (99.4%)	930 (99.6%)
Safety Population	622 (99.7%)	308 (99.4%)	930 (99.6%)
Per-Protocol Population	578 (92.6%)	286 (92.3%)	864 (92.5%)

The database lock date was 10 Dec 2019.
Abbreviations: mITT = modified intent-to-treat; N = number of patients in the treatment group.
Percentages are based on the total number of patients in all randomized patients for each treatment group or total.

For the Final Analysis Population of all randomized patients, the number of patients included in each analysis set is presented in Table 15.

Table 15. Number of Patients in Each Analysis Population by Treatment Group (All Randomized Patients) – Final Analysis

Patient Population	Relugolix (N = 719)	Leuprolide (N = 359)	Total (N = 1078)
mITT Final Analysis Population	717 (99.7%)	357 (99.4%)	1074 (99.6%)
mITT Metastatic Patient Population	290 (40.3%)	144 (40.1%)	434 (40.3%)
Final Analysis Safety Population	717 (99.7%)	357 (99.4%)	1074 (99.6%)
Metastatic Patient Safety Population	290 (40.3%)	144 (40.1%)	434 (40.3%)

The database lock date was 23 Sep 2020.
Abbreviations: mITT = modified intent-to-treat; N = number of patients in the treatment group.
Percentages are based on the total number of patients in all randomized patients for each treatment group or total.

Outcomes and estimation

Primary efficacy endpoint – sustained castration rate

This study had two separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing efficacy (Table 9). The study successfully met its primary endpoint based on both evaluation criteria.

A summary of the primary endpoint analysis is presented in Table 16. An overview of the Kaplan-Meier- Analysis for sustained castration rate is presented by treatment group in Figure 14.

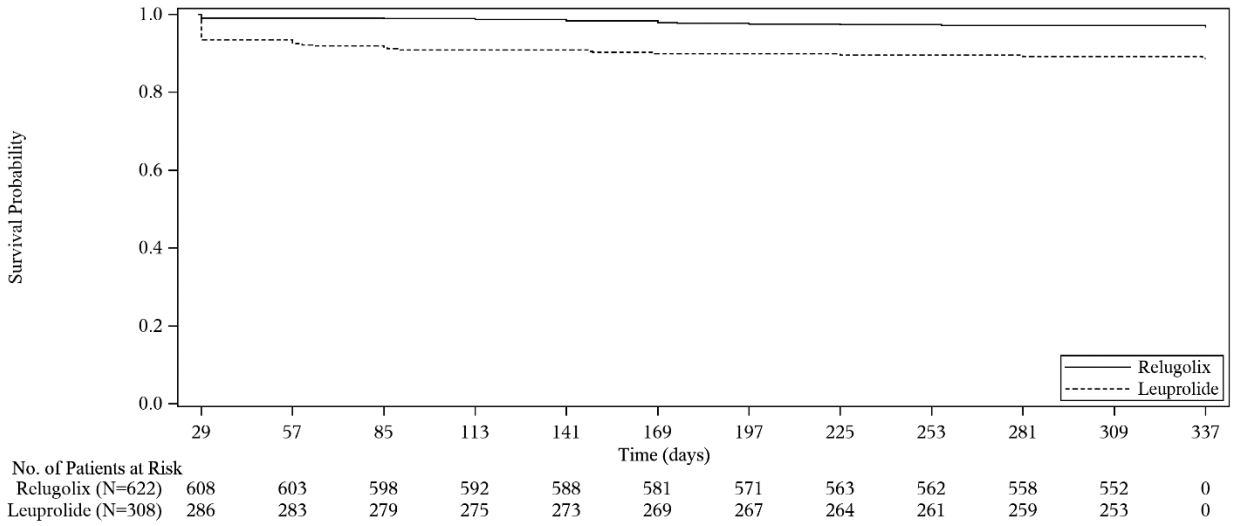
For sensitivity and subgroup analyses, see **Ancillary analyses**.

Table 16. 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		
Evaluation Criterion 1		
Castration rate at Day 337 (95% CI) [a]	96.7% (94.9%, 97.9%)	88.8% (84.6%, 91.8%)
Evaluation Criterion 2		
Difference from leuprolide at Day 337 (95% CI) [b]	7.9% (4.1%, 11.8%)	
p-value [c]	<0.0001	
Hazard ratio to leuprolide [d] (95% CI)	0.2621 (0.1489, 0.4613)	

Abbreviations: CI = confidence interval; 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.
[b] 95% CI for treatment difference was calculated by linear transformation of the difference in survival function.
[c] Unstratified test statistics via log-log transformation of the difference in survival function at a fixed time point was performed.
[d] Hazard ratio in comparison of relugolix to leuprolide was performed using Cox proportional hazard model.
The non-inferiority margin for the difference from leuprolide was −10%.

Figure 14. Kaplan-Meier Survival Curve of Sustained Castration Rate (< 50 ng/dL) (mITT Population)



Abbreviations: mITT = modified intent-to-treat.

Key secondary efficacy endpoints

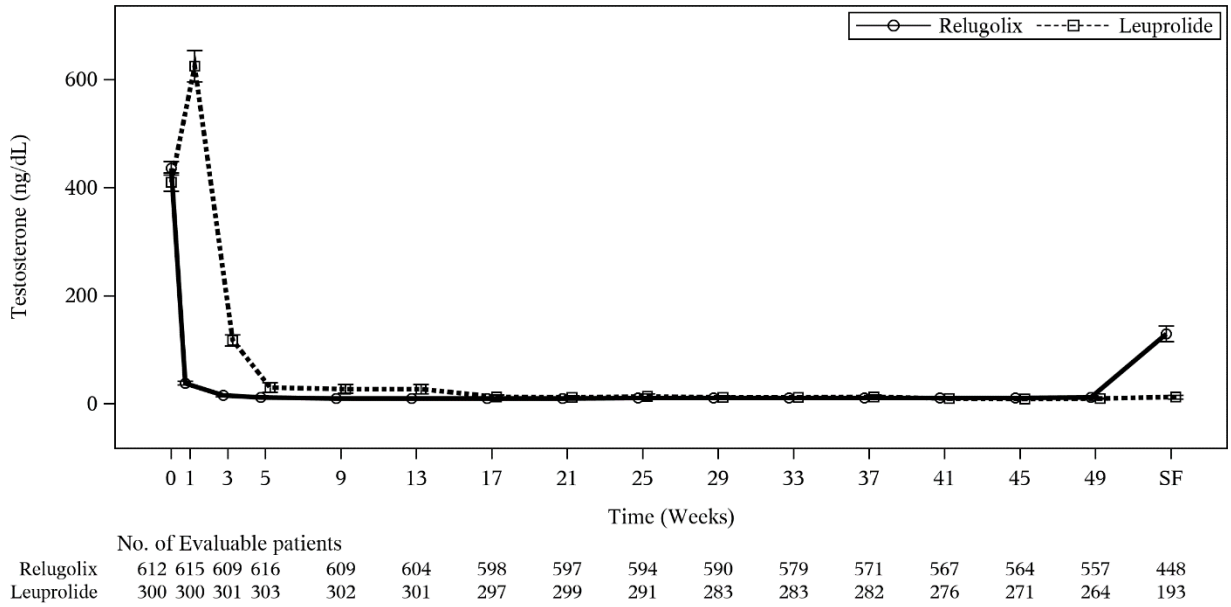
See Table 9 for an overview of all key (and other) secondary endpoints, and Table 10 for the hierarchical testing order and timing of analysis for the key secondary endpoints.

Key secondary efficacy endpoint – castration rate at Week 1 Day 4 (Day 4)

Key secondary efficacy endpoint – castration rate at Week 3 Day 1 (Day 15)

Testosterone concentrations over time are presented in Figure 15.

Figure 15. Testosterone Concentrations Over Time (mITT Population)



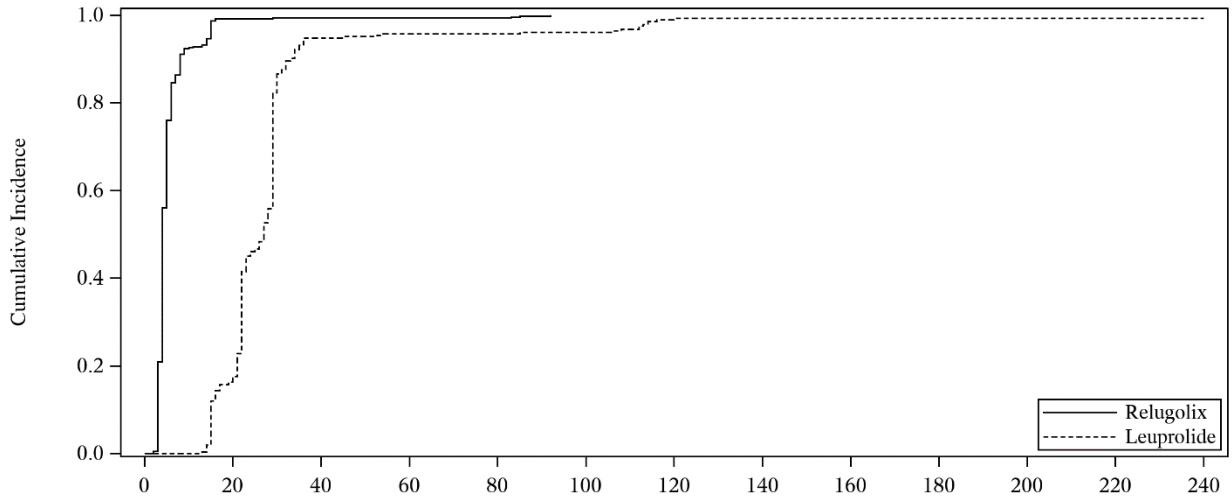
No. of Evaluable patients																
Relugolix	612	615	609	616	609	604	598	597	594	590	579	571	567	564	557	448
Leuprolide	300	300	301	303	302	301	297	299	291	283	283	282	276	271	264	193

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SF = Safety follow up.
Mean (95% CI) are presented.

The cumulative incidence of time to initial castration (testosterone < 50 ng/dL) is presented in

Figure 16, and Kaplan-Meier estimates are provided in Table 17.

Figure 16. Cumulative Incidence of Time to Initial Castration (Testosterone < 50 ng/dL) (mITT Population)



No. of Patients at Risk													
Relugolix	622	5	4	3	3	0	0	0	0	0	0	0	0
Leuprolide	308	256	16	13	12	11	3	2	1	1	1	1	0

The database lock date was 10 Dec 2019.
Abbreviation: mITT = modified intent-to-treat.

Table 17. Kaplan-Meier Estimates for Time to Initial Castration (Testosterone < 50 ng/dL) (mITT Population)

	Relugolix (N = 622)	Leuprolide (N = 308)
Time to initial castration in days[a]		
No. of events (%)	620 (99.7)	303 (98.4)
No. of censored (%)	2 (0.3)	5 (1.6)
Median (95% CI)[b]	4.0 (NE, NE)	27.0 (23.0, 28.0)
Q1, Q3	4.0, 5.0	22.0, 29.0
Kaplan-Meier estimates, %		
Castration rate at Day 4 (95% CI)[b]	56.04 (52.18, 59.97)	0.00 (NE, NE)
Difference from leuprolide (95% CI)[c]	56.04 (NE, NE)	
p-value[d]	<0.0001/<0.0001	
Castration rate at Day 15 (95% CI)[b]	98.71 (97.56, 99.39)	12.05 (8.88, 16.25)
Difference from leuprolide (95% CI)[c]	86.66 (82.91, 90.41)	
p-value[d]	<0.0001/<0.0001	
Castration rate at Day 29 (95% CI)[b]	99.36 (98.43, 99.78)	82.35 (77.87, 86.38)
Difference from leuprolide (95% CI)[c]	17.01 (12.69, 21.33)	

Abbreviations: CI = confidence interval; EDC = electronic data capture; IWRS = interactive voice/web recognition system; mITT = modified intent-to-treat; NE = not estimable; Q1 = 25th percentile; Q3 = 75th percentile.
[a] Time to initial castration is defined as time from the date of first dose to the date of initial testosterone suppression to < 50 ng/dL.
[b] 95% CI in each treatment group is calculated by log-log transformation of survival function in each treatment group.
[c] 95% CI of treatment difference is calculated by linear transformation of the difference in survival function.
[d] Stratified test statistics (stratification factors per EDC [primary]/IWRS [sensitivity], respectively) via log-log transformation of the difference in survival function at a fixed time point is performed. If such test statistics is not estimable, stratified version of Mantel-Haenszel test using pooled Kaplan-Meier estimator in each stratum is constructed.

Key secondary efficacy endpoint – PSA response by Week 3 Day 1 (Day 15) through Week 5 Day 1 (Day 29)

A summary of status of PSA response, defined as a > 50% reduction in PSA from baseline at Week 3 Day 1 and confirmed by a second evaluation (at Week 5 Day 1) according to Scher et al. 2016, is provided in Table 18.

Table 18. Response Status of Prostate-Specific Antigen (mITT Population)

	Relugolix (N = 622)		Leuprolide (N = 308)		
	n (%)	95% CI[a]	n (%)	95% CI[a]	p-value[b]
Week 3 Day 1					
> 50% reduction from baseline	498 (80.1)	76.70, 83.14	62 (20.1)	15.80, 25.05	
Week 5 Day 1					
> 50% reduction from baseline	588 (94.5)	92.44, 96.19	244 (79.2)	74.26, 83.61	
> 50% reduction at Week 3 Day 1 and confirmed at Week 5 Day 1	494 (79.4)	76.03, 82.53	61 (19.8)	15.50, 24.70	<0.0001/<0.0001

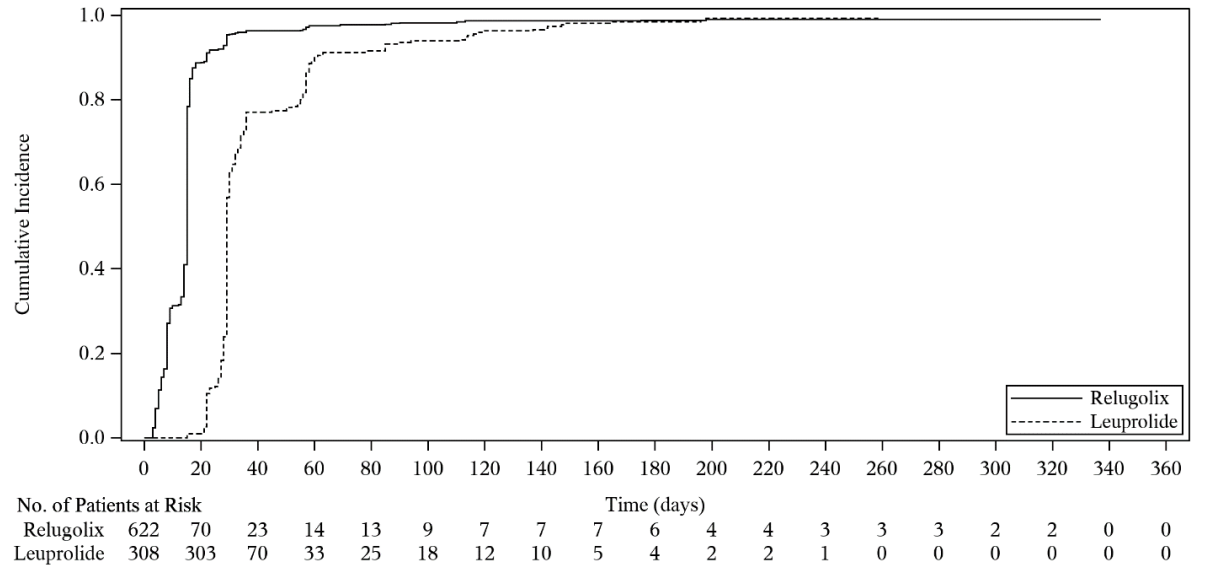
Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; N = number of patients in the treatment group; PSA = prostate-specific antigen.
[a] 95% exact CI is provided. Patients without PSA assessment are considered as non-responders.
[b] Comparison of relugolix with leuprolide was performed using stratified Cochran-Mantel-Haenszel test (stratification factors per electronic data capture).

Key secondary efficacy endpoint – profound castration rate at Week 3 Day 1 (Day 15)

The cumulative incidence of time to profound castration (testosterone < 20 ng/dL) is presented in Figure 17, and Kaplan-Meier estimates are provided in

Table **19**.

Figure 17. Cumulative Incidence of Time to Initial Profound Castration (Testosterone < 20 ng/dL) (mITT Population)



Abbreviation: mITT = modified intent-to-treat.

Table 19. Kaplan-Meier Estimates for Time to Profound Castration (Testosterone < 20 ng/dL) (mITT Population)

	Relugolix (N = 622)	Leuprolide (N = 308)
Time to initial profound testosterone castration in days[a]		
No. of events (%)	612 (98.4)	302 (98.1)
No. of censored (%)	10 (1.6)	6 (1.9)
Median (95% CI)[b]	15.0 (NE, NE)	29.0 (NE, NE)
Q1, Q3	8.0, 15.0	29.0, 36.0
Kaplan-Meier estimates, %		
Castration rate at Day 4 (95% CI)[b]	6.92 (5.18, 9.22)	0.00 (NE, NE)
Difference from leuprolide (95% CI)[c]	6.92 (NE, NE)	
Castration rate at Day 15 (95% CI)[b]	78.38 (75.06, 81.53)	0.98 (0.32, 3.00)
Difference from leuprolide (95% CI)[c]	77.41 (73.98, 80.83)	
p-value[d]	<0.0001	

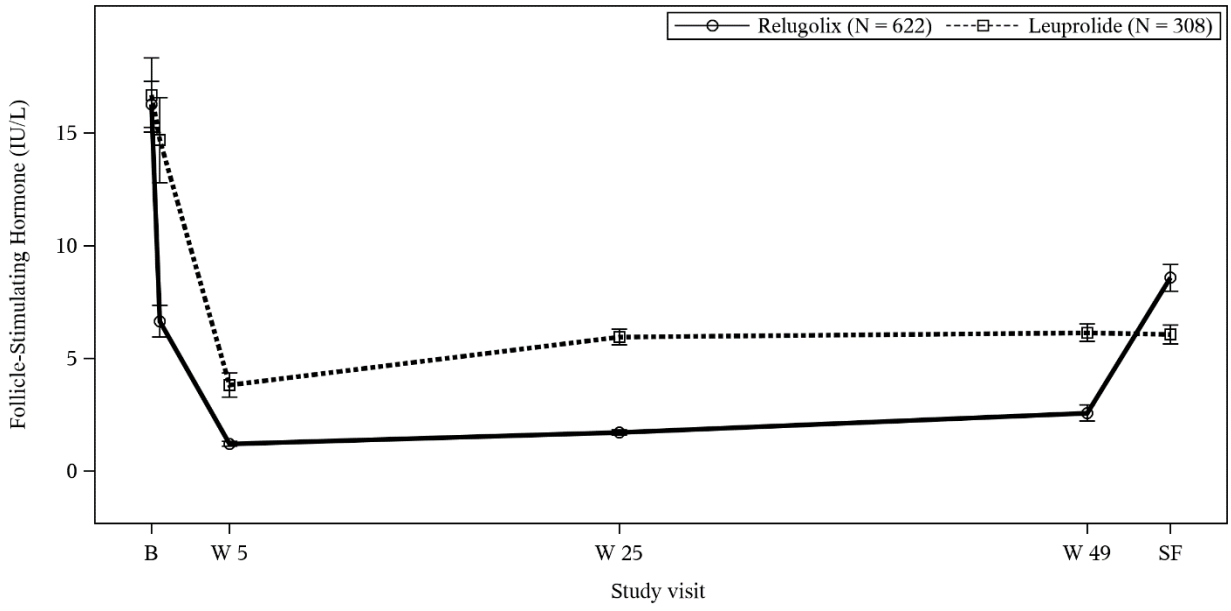
Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; NE = not estimable; Q1 = 25th percentile; Q3 = 75th percentile.
[a] Time to initial profound testosterone castration was defined as time from the date of first dose to the date of initial testosterone suppression to < 20 ng/dL.
[b] 95% CI in each treatment group was calculated by log-log transformation of survival function in each treatment group.
[c] 95% CI of treatment difference was calculated by linear transformation of the difference in survival function.
[d] Unstratified test statistics via log-log transformation of the difference in survival function at a fixed time point was performed.

Key secondary efficacy endpoint – FSH at Week 25 Day 1 (Day 169)

The follicle-stimulating hormone (FSH) concentrations over time are presented by visit in Figure 18.

Levels of FSH were suppressed to a greater degree by relugolix than by leuprolide at Week 25 Day 1 (Day 169). In the relugolix group, the mean (SD) FSH concentration was 1.72 (1.376) IU/L, with a mean (SD) percent change from baseline of 86.32% (10.699%). In the leuprolide group, the mean (SD) FSH concentration was 5.95 (3.071) IU/L, with a mean (SD) percent change from baseline of -47.53% (32.560%). The difference was statistically significant (p < 0.0001).

Figure 18. Follicle-Stimulating Hormone Concentrations Over Time (mITT Population)



Abbreviations: B = baseline; CI = confidence interval; mITT = modified intent-to-treat; W = week.
Mean (95% CI) are presented.

Key secondary efficacy endpoint – castration resistance-free survival in patients with metastatic prostate cancer

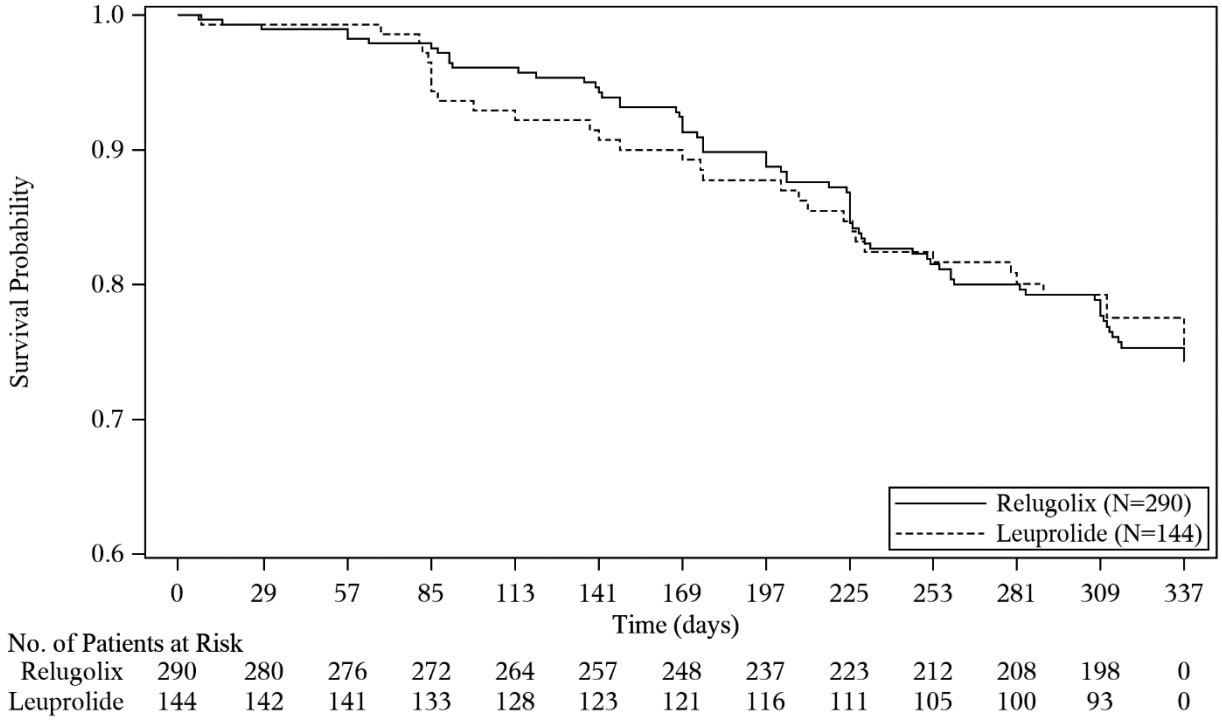
Key secondary efficacy endpoint – castration resistance-free survival in all patients

The key secondary endpoint of castration-resistance free survival (CRFS) was tested at the final analysis, both in patients with metastatic prostate (mITT metastatic patient population) cancer and in all patients (mITT Final Analysis Population), see also Table 10 and Table 15.

The Kaplan-Meier survival curve of **CRFS in metastatic patients** is provided in

Figure 19 and the Kaplan-Meier estimates are provided in Table 20.

Figure 19. Kaplan-Meier Survival Curve of Castration Resistance-Free Survival in Metastatic Patients (mITT Metastatic Patient Population)



The database lock date was 23 Sep 2020.
Abbreviation: mITT = modified intent-to-treat; N = number of patients in the treatment group.

Table 20. Kaplan-Meier Estimates for Castration Resistance-Free Survival in Metastatic Patients (mITT Metastatic Patient Population)

	Relugolix (N = 290)	Leuprolide (N = 144)
Time to castration resistance-free survival		
No. of events (%)	68 (23.4)	32 (22.2)
Due to PSA progression	67 (23.1)	28 (19.4)
Due to on-treatment death	1 (0.3)	4 (2.8)
No. of censored (%)	222 (76.6)	112 (77.8)
Median (95% CI)[a]	NE (NE, NE)	NE (NE, NE)
Q1, Q3	337.0, NE	NE, NE

Kaplan-Meier estimates on

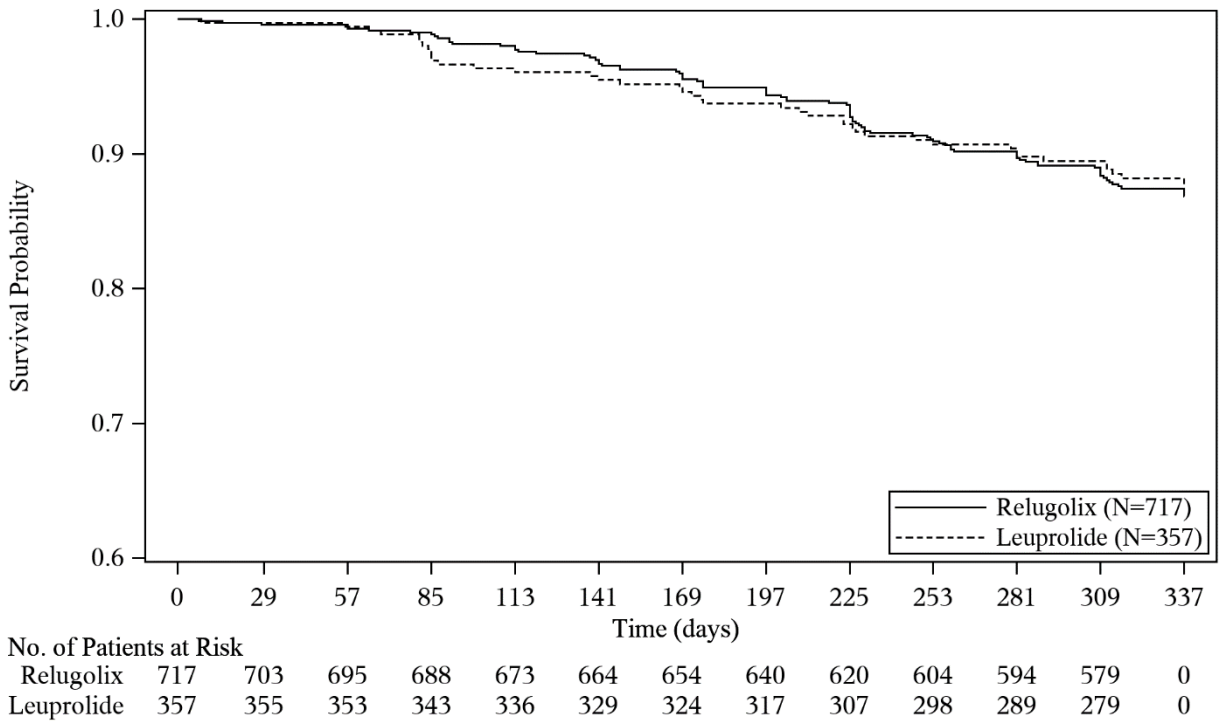
	Relugolix (N = 290)	Leuprolide (N = 144)
Resistance-free rate at Day 337 (95% CI)[a]	74.31 (68.56, 79.17)	75.27 (66.71, 81.93)
Difference from leuprolide (95% CI)[b]	-0.96 (-10.20, 8.28)	
Hazard ratio to leuprolide (95% CI)[c]	1.0319 (0.6774, 1.5719)	
p-value[d]	0.8405/0.8491	

The database lock date was 23 Sep 2020.
Abbreviations: CI = confidence interval; EDC = electronic data capture; IWRS = interactive voice/web recognition system; mITT = modified intent-to-treat; N = number of patients in the treatment group; NE = not estimable; PSA = prostate-specific antigen; Q1 = 25th percentile; Q3 = 75th percentile.
[a] 95% CI in each treatment group is calculated by log-log transformation of survival function in each treatment group.
[b] 95% CI for treatment difference is calculated by linear transformation of the difference in survival function.
[c] Hazard ratio in comparison of relugolix to leuprolide is performed using Cox proportional hazard model.
[d] p-value is based on stratified (stratification factors per EDC [primary]/per IWRS [sensitivity], respectively) log-rank test.

According to the testing strategy (Table 10), **CRFS in all patients** (with or without metastatic prostate cancer) was not formally tested at the final analysis, because the results in the subgroup of metastatic patients did not achieve statistical superiority (see above). This endpoint was thus analysed as exploratory.

The Kaplan-Meier survival curve of CRFS in all patients is provided in Figure 20. and the Kaplan-Meier estimates are provided in Table 21.

Figure 20. Kaplan-Meier Survival Curve of Castration Resistance-Free Survival All Patients (With or Without Metastatic Prostate Cancer) (mITT Final Analysis Population)



The database lock date was 23 Sep 2020.
Abbreviation: mITT = modified intent-to-treat; N = number of patients in the treatment group.

Table 21. Kaplan-Meier Estimates for Castration Resistance-Free Survival in All Patients (mITT Final Analysis Population)

	Relugolix (N = 717)	Leuprolide (N = 357)
Time to castration resistance-free survival		
No. of events (%)	88 (12.3)	42 (11.8)
Due to PSA progression	87 (12.1)	35 (9.8)
Due to on-treatment death	1 (0.1)	7 (2.0)
No. of censored (%)	629 (87.7)	315 (88.2)
Median (95% CI)[a]	NE (NE, NE)	NE (NE, NE)
Q1, Q3	NE, NE	NE, NE
Kaplan-Meier estimates on		
Resistance-free rate at day 337 (95% CI)[a]	86.82 (84.00, 89.18)	87.33 (83.21, 90.50)
Difference from leuprolide (95% CI)[b]	-0.50 (-4.94, 3.93)	
Hazard ratio to leuprolide (95% CI)[c]	1.0335 (0.7154, 1.4930)	
Nominal p-value[d]	0.8937/0.8671	

The database lock date was 23 Sep 2020.
Abbreviations: CI = confidence interval; EDC = electronic data capture; IWRS = interactive voice/web recognition system; mITT = modified intent-to-treat; N = number of patients in the treatment group; NE = not estimable; PSA = prostate-specific antigen; Q1 = 25th percentile; Q3 = 75th percentile.
[a] 95% CI in each treatment group is calculated by log-log transformation of survival function in each treatment group.
[b] 95% CI for treatment difference is calculated by linear transformation of the difference in survival function.
[c] Hazard ratio in comparison of relugolix to leuprolide is performed using Cox proportional hazard model.
[d] p-value is based on stratified (stratification factors per EDC [primary]/per IWRS [sensitivity], respectively) log-rank test.

Key secondary efficacy endpoint – testosterone recovery (back to > 280 ng/dL)

As the enrolment for the follow-up of testosterone recovery had been completed for the patients enrolled under protocol Amendment 2, an analysis of time to testosterone recovery back to > 280 ng/dL at the 90-day follow-up was performed at the primary analysis, but for exploratory purposes without formal testing. Though, because the results for CRFS in patients with metastatic disease did not achieve statistical superiority (see above), testosterone recovery was not to be formally tested/was to be analysed as exploratory at the primary analysis as well (see testing order and timing of analysis in Table 10.

By the 90-day follow-up visit, 43.8% (60/137) of patients in the relugolix group compared with 4.3% (2/47 patients) in the leuprolide group had testosterone recovery to > 280 ng/dL.

Other secondary efficacy endpoints

For brevity, the results for the other (non-key) secondary efficacy endpoints (that were not part of the hierarchical testing order) are not reported here, except for the impact of treatment on measures of patient reported outcomes/quality of life, which is reported in a concise manner.

Other secondary efficacy endpoint – patient-reported outcomes/quality of life

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

In general, there were no notable differences between treatment groups in the results of the **EORTC-QLQ-PR25** assessments that were clinically meaningful or unexpected during treatment on study. At the 90-day follow-up visit, the score for the hormonal treatment-related symptoms domain was numerically lower in the relugolix group compared with the leuprolide group, indicating less severity of hormonal treatment-related symptoms. However, the mean scores of sexual activity and of sexual functioning were similar between the two treatment groups at the 90-day follow-up visit, and all other domains in the assessment (urinary symptoms, incontinence aid use, and bowel symptoms) were comparable between the two treatment groups as well.

Regarding the results of the of the **EQ-5D-5L** assessments, the proportions of patients who had deterioration, no change or improvement in each domain, were similar across the two treatment groups throughout the study. The visual analog scores (VAS) were also similar across the two treatment groups.

Exploratory efficacy endpoint – overall survival

For brevity, the results for this exploratory efficacy endpoint are reported in a concise manner. Refer to the Clinical AR for more information/results.

The survival rates (95% CI) at Day 337 were 0.9885 (0.9761, 0.9945) in the relugolix group and 0.9740 (0.9486, 0.9869) in the leuprolide group, with a difference of 0.0146 (0.0051, 0.0343). The 22 deaths in the overall survival analysis comprise 16 patients who died due to a treatment emergent AE during the study (see Clinical safety), one patient who died after the AE reporting period, and five patients reported during the health status survey as having died after the study and before database lock (four in the relugolix group and one patient in the leuprolide group).

Ancillary analyses

Primary efficacy endpoint – sustained castration rate

Sensitivity analyses

A total of four pre-specified sensitivity analyses were conducted to test the robustness of the primary analyses (for both Criterion 1 and Criterion 2), see also ***Statistical methods***. The results of these sensitivity analyses of the primary endpoint are provided in Table 22.

Table 22. Sensitivity Analyses of Kaplan-Meier Estimates for Sustained Castration Rate from Day 29 to Day 337 (mITT Population)

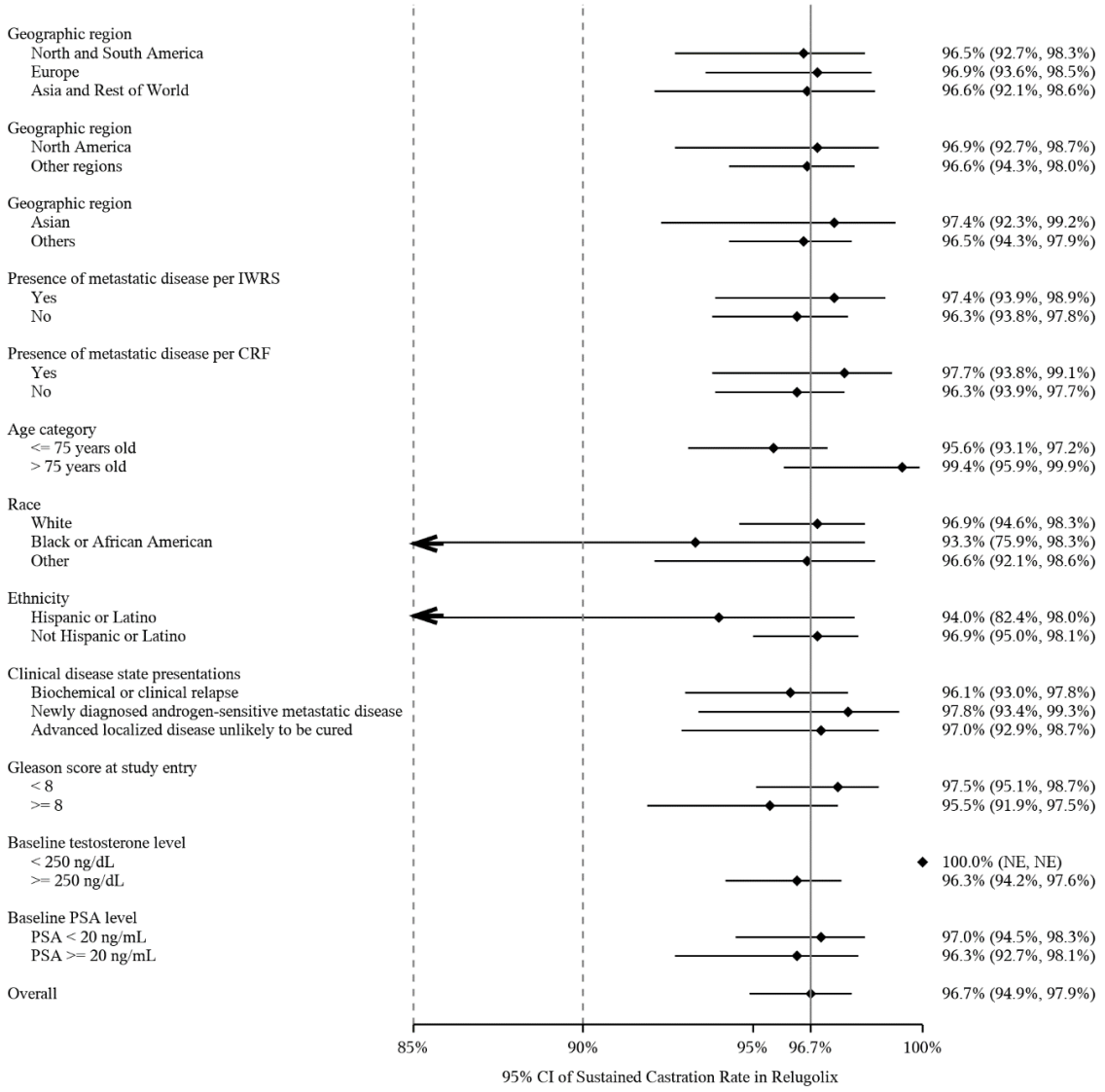
	Relugolix				Leuprolide			
	No. at Risk[a]	**Testosterone ≥ 50 ng/dL[b]**	**Censored**	**Cumulative Probability[c]**	**No. at Risk[a]**	**Testosterone ≥ 50 ng/dL[b]**	**Censored**	**Cumulative Probability[c]**
Sensitivity 1								
Per-protocol population	578				286			
Day 337	0	19	559	96.5%	0	29	257	89.7%
95% CI at Day 337[d]				(94.5%, 97.7%)				(85.4%, 92.7%)
Difference from leuprolide at Day 337				6.8%				
95% CI for difference from leuprolide at Day 337[e]				(2.9%, 10.7%)				
p-value[f]				0.0002				
Hazard ratio to leuprolide (95% CI)[g]				0.3092 (0.1727, 0.5535)				
Sensitivity 2								
mITT population	622				308			
Day 1	591	0	31	100.0%	214	0	94	100.0%
Day 337	0	17	574	96.9%	0	22	192	89.6%
95% CI at Day 337[d]				(95.0%, 98.1%)				(84.6%, 93.0%)
Difference from leuprolide at Day 337				7.3%				
95% CI for difference from leuprolide at Day 337[e]				(2.9%, 11.7%)				
p-value[f]				0.0001				
Hazard ratio to leuprolide (95% CI)[g]				0.2664 (0.1409, 0.5035)				
Sensitivity 3								
mITT population	622				308			
Day 337	0	69	553	88.6%	0	50	258	83.7%
95% CI at Day 337[d]				(85.8%, 90.9%)				(79.0%, 87.4%)
Difference from leuprolide at Day 337				5.0%				
95% CI for difference from leuprolide at Day 337[e]				(0.1%, 9.8%)				
p-value[f]				0.0368				
Hazard ratio to leuprolide (95% CI)[g]				0.6461 (0.4476, 0.9326)				
Sensitivity 4								
mITT population	622				308			
Day 337	0	15	607	97.3%	0	17	291	94.0%
95% CI at Day 337[d]				(95.6%, 98.4%)				(90.5%, 96.2%)
Difference from leuprolide at Day 337				3.3%				
95% CI for difference from leuprolide at Day 337[e]				(0.2%, 6.4%)				
p-value[f]				0.0202				
Hazard ratio to leuprolide (95% CI)[g]				0.4124 (0.2058, 0.8263)				

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat.
Sensitivity analysis 1 was performed under per-protocol population. Sensitivity analysis 2 was performed to consider patients who had received concomitant medications and herbal supplements that could possibly affect testosterone level as censored at Day 1. Day 1 data are included to show sample size. Sensitivity analysis 3 was performed to consider patients who had missed two or more consecutive visits after Week 5 Day 1 or discontinued early as having an event. Sensitivity analysis 4 was performed to consider censoring patients who had not reached castrate level at Week 5 Day 1.
[a] Number of patients at risk.
[b] Cumulative number of patients with testosterone ≥ 50 ng/dL.
[c] Cumulative probability = Estimated probability of testosterone values < 50 ng/dL.
[d] The 95% CI in each treatment group was calculated by log-log transformation of survival function in each treatment group.
[e] The 95% CI for treatment difference was calculated by linear transformation of the difference in survival function.
[f] Unstratified test statistics via log-log transformation of the difference in survival function at a fixed time point were performed.
[g] Hazard ratio in comparison of relugolix to leuprolide was performed using Cox proportional hazard model.

Subgroup analyses

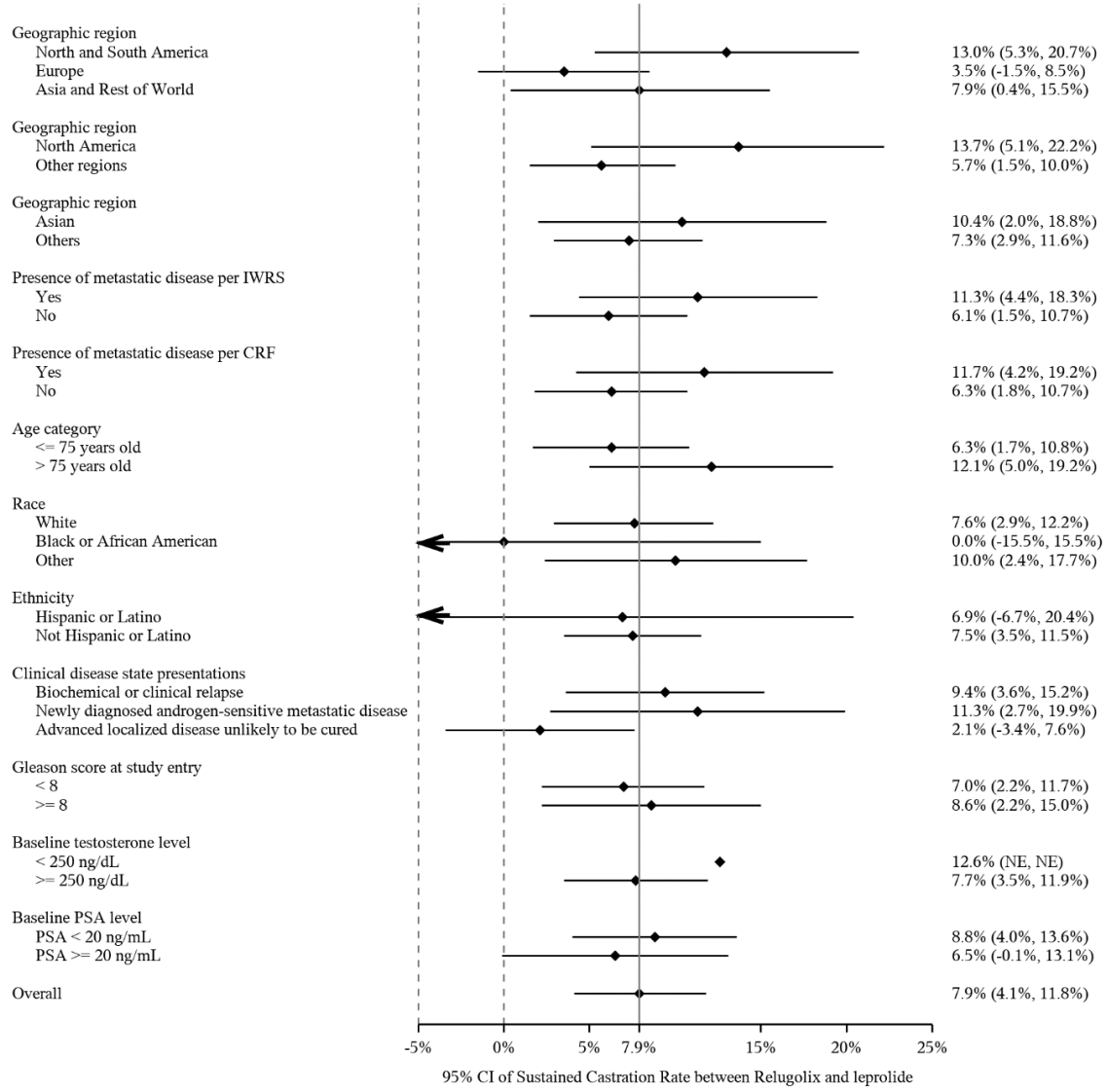
The results of the subgroup analyses for Evaluation Criterion 1 (sustained castration rate) are presented in Figure 21. The results of the subgroup analyses for Evaluation Criterion 2 (non-inferiority of relugolix compared with leuprolide) are presented in Figure 22.

Figure 21. Subgroup Analysis for Sustained Castration Rate (Evaluation Criterion 1) (mITT Population)



Abbreviations: CI = confidence interval; CRF = case report form; 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.
Evaluation Criterion 1: to determine whether the sustained castration rate (defined as the cumulative probability of testosterone suppression to < 50 ng/dL while on study drug from Week 5 Day 1 through Week 49 Day 1) for relugolix is ≥ 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group was calculated and must have been at least 90% for this criterion to have been met.

Figure 22. Subgroup Analysis for Differences in Sustained Castration Rates (Evaluation Criterion 2) (mITT Population)



Abbreviations: CI = confidence interval; CRF = case report form; IWRS = interactive voice/web recognition system; mITT = modified intent-to-treat; PSA = prostate-specific antigen.
← : 95% CI of sustained castration rate is extending to -15.5% in Black or African American and to -6.7% in Hispanic or Latino.
Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide every 3-month depot injection as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the two treatment groups was calculated and must have been greater than or equal to the non-inferiority margin of -10% for this criterion to have been met.

The above figures do not show the results of the subgroup analysis for the different leuprolide dose levels (22.5 mg vs 11.25 mg) in the leuprolide group. These, i.e. the testosterone castration rates at Week 49 Day 1 (Day 337) for the two different dose levels in the leuprolide group and their 95% CIs, are provided separately in below Table 23.

Table 23. Subgroup Analysis of Kaplan-Meier Estimates for Sustained Castration Rate for Different Leuprolide Dose Levels (mITT Population)

	Relugolix				Leuprolide			
	No. at Risk[a]	Testosterone >= 50 ng/dL[b]	Censored	Cumulative Probability[c]	No. at Risk[a]	Testosterone >= 50 ng/dL[b]	Censored	Cumulative Probability[c]
Does level in Leuprolide								
11.25 mg					44			
Day 337					0	3	41	93.1%
95% CI at Day 337[d]								(80.0%, 97.7%)
22.5 mg					264			
Day 337					0	31	233	88.0%
95% CI at Day 337[d]								(83.4%, 91.4%)

The database lock date was 10 Dec 2019.
Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; NE = not estimable.
[a]Number of patients at risk.
[b]Cumulative number of patients with testosterone >= 50 ng/dL.
[c]Cumulative probability = Estimated probability of testosterone values < 50 ng/dL.
[d]95% CI in each treatment group is calculated by log-log transformation of survival function in each treatment group.

Summary of main efficacy results

Table 24 summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

Table 24. Summary of efficacy for trial MVT-601-3201

Title: HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer		
Study identifier	Study Number: MVT-601-3201 EudraCT Number: 2017-000160-15 NCT Number: NCT03085095 Full text publication: Shore et al. N Engl J Med. 2020	
Design (Figure 12)	Randomized (2:1), multinational, open-label, parallel grouped, efficacy and safety study	
	Duration of main phase: Duration of run-in phase: Duration of extension	48 weeks (treatment period) 28 days (screening period) 30 days (follow-up period)
Hypothesis	Non-inferiority	
Treatments groups	**Relugolix**	360 mg (3 × 120 mg tablets) single oral loading dose on Day 1 followed by one 120 mg tablet orally once daily for 48 weeks, n = 624
	Leuprolide	3-month (3-M) depot injection, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) every 12 weeks for 48 weeks, n = 308

Endpoints and definitions (Table 9)	Primary endpoint	F1	Sustained castration rate, defined as the cumulative probability of testosterone suppression to castrate levels of < 50 ng/dL (1.7 nmol/L) while on study treatment from Week 5 Day 1 (study Day 29) through Week 49 Day 1 (study Day 337). • Evaluation Criterion 1: to determine whether the sustained castration rate (defined as the cumulative probability of testosterone suppression to < 50 ng/dL while on study drug from Week 5 Day 1 through Week 49 Day 1) for relugolix is ≥ 90%. The lower bound of the 95% confidence interval for the cumulative probability of sustained testosterone suppression in the relugolix treatment group was calculated and must be at least 90% for this criterion to be met. • Evaluation Criterion 2: to establish the non-inferiority of relugolix compared to leuprolide every 3-month depot injection as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% confidence interval for the difference in the cumulative probability of sustained testosterone suppression between the two treatment groups was calculated and must be greater than or equal to the non-inferiority margin of -10% for this criterion to be met.
	Key Secondary Endpoint – Primary analysis	F2_1	Castration rate on Week 1 Day 4
	Key Secondary Endpoint – Primary analysis	F2_2	Castration rate on Week 3 Day 1
	Key Secondary Endpoint – Primary analysis	F2_3	Confirmed prostate-specific antigen (PSA) response rate at Week 3 Day 1 followed with confirmation at Week 5 Day 1
	Key Secondary Endpoint – Primary analysis	F2_4	Profound castration rate at Week 3 Day 1
	Key Secondary Endpoint – Primary analysis	F2_5	Follicle-stimulating hormone (FSH) level at Week 25 Day 1
	Key Secondary Endpoint[a]	F2_6	Time to testosterone recovery back to > 280 ng/dL at the 90-day follow-up in patients participating in testosterone recovery follow-up
Note	[a] Time to testosterone recovery was performed at the primary analysis for exploratory purposes without formal testing. Testing order of time to testosterone recovery in the final analysis was to be preceded by castration resistance-free survival (see Table 10); however, the testosterone recovery analysis was not formally tested at the final analysis, because the results for castration resistance-free survival did not achieve statistical superiority.		

Database lock	10-Dec-2019 (primary analysis)			
Results and Analysis				
Analysis description	**Primary endpoint of primary analysis**			
Analysis population and time point description	Modified intent-to-treat (mITT) population[a] Sustained castration rate (< 50 ng/dL) from Week 5 Day 1 (study Day 29) through Week 49 Day 1 (study Day 337).			
Descriptive statistics and estimate variability	**Treatment group**	**Relugolix**	**Leuprolide**	
	Number of patients	622	308	
	Evaluation Criterion 1[b]			
	Castration rate from Week 5 Day 1 (Day 29) to Week 49 Day 1	96.7%	88.8%	
	(95% CI)	(94.9%, 97.9%)	(84.6%, 91.8%)	
	Evaluation Criterion 2[b]			
	Difference from leuprolide at Week 49 Day 1 (Day337)	7.9%		
	(95% CI)	(4.1%, 11.8%)		
	p-value	<0.0001		
	Hazard ratio to leuprolide	0.2621		
	(95% CI)	(0.1489, 0.4613)		
Notes	[a] Except for four patients who did not receive study drug (two patients in each treatment group), all randomized patients were included in the mITT. [b] Study MVT-601-3201 had two separate evaluation criteria for the primary efficacy endpoint to support different global regulatory requirements for assessing benefit: • Evaluation Criterion 1 was a regulatory requirement from the FDA and was the trial success criterion for the primary efficacy endpoint. • Evaluation Criterion 2, the primary efficacy endpoint required by EMA, was the first to be tested in the order of ranked key secondary endpoints to assess non-inferiority of relugolix compared with leuprolide after Evaluation Criterion 1 was passed.			
Analysis description	**Key secondary endpoints of primary analysis (F2_1, F2_2, F2_3, F2_4, F2_5, and F2_6), pre-specified**			
Analysis population and time point description	mITT population Time point description: see endpoints.			
Descriptive statistics and estimate variability	**Treatment Group / Endpoint**	**Relugolix**	**Leuprolide**	**p-value**

	Cumulative probability of testosterone suppression < 50 ng/dL prior to dosing on Week 1 Day 4	56.04% (95% CI: 52.18, 59.97)	0.00% (95% CI: NE, NE)	<0.0001
	Cumulative probability of testosterone suppression < 50 ng/dL prior to dosing on Week 3 Day 1	98.71% (95% CI: 97.56, 99.39)	12.05% (95% CI: 8.88, 16.25)	<0.0001
	Proportion of patients with PSA response at Week 3 Day 1 followed with confirmation at Week 5 Day 1	79.4% (95% CI: 76.03, 82.53)	19.8% (95% CI: 15.50, 24.70)	<0.0001
	Cumulative probability of testosterone suppression < 20 ng/dL prior to dosing on Week 3 Day 1	78.38% (95% CI: 75.06, 81.53)	0.98% (95% CI: 0.32, 3.00)	<0.0001
	Mean FSH (IU/L) at Week 25 Day 1	1.72 (SD: 1.376)	5.95 (SD: 3.071)	<0.0001
	Cumulative incidence of time to testosterone recovery back to > 280 ng/dL at the 90-day follow-up in patients participating in testosterone recovery follow-up[a]	53.93% (95% CI: 45.20, 63.16)	3.23% (95% CI: 0.46, 20.77)	0.0017[b]
Notes	[a] Time to testosterone recovery was assessed in a subset of 137 vs 47 patients. [b] Time to testosterone recovery was performed at the primary analysis for exploratory purposes without formal testing. Testing order of time to testosterone recovery in the final analysis was to be preceded by castration resistance-free survival (see Table 10); however, the testosterone recovery analysis was not formally tested at the final analysis, because the results for castration resistance-free survival did not achieve statistical superiority.			
Abbreviations: CI = confidence interval; NE = not estimable; SD = standard deviation.				

2.6.5.3. Clinical studies in special populations

Consistent efficacy results (results not shown) were observed across subgroups of age category (≤ 65 years, > 65 years, ≤ 75 years, >75 years), BMI (< 25, 25 to <30, ≥ 30 kg/m^2), renal function

(normal, mildly impaired, moderately/severely impaired), alcohol consumption (no, moderate, heavy use) or smoking history (never, former, current smoker).

The number of patients in the pivotal study aged ≤ 75 or > 75 years old is shown in

Table 12 (specified per treatment group). Below Table 25 shows the numbers of patients in all specified age categories > 65 years old across the relugolix prostate cancer program studies.

Table 25. Number of Elderly Patients across Relugolix Prostate Cancer Program Studies (mITT Population)

	Age 65-74 (N = 575)		**Age 75-84 (N = 372)**		**Age 85+ (N = 46)**		**Total (N = 993)**	
	Relugolix (N = 393)	**Comparator (N = 182)**	**Relugolix (N = 268)**	**Comparator (N = 104)**	**Relugolix (N = 31)**	**Comparator (N = 15)**	**Relugolix (N = 692)**	**Comparator (N = 301)**
Controlled Trials	371 (94.4%)	182 (100.0%)	247 (92.2%)	104 (100.0%)	31 (100.0%)	15 (100.0%)	649 (93.8%)	301 (100.0%)
Non-controlled trials	22 (5.6%)	0	21 (7.8%)	0	0	0	43 (6.2%)	0

Percentages are based on the total number of elderly patients in controlled trials and non-controlled trial.
Controlled studies include study C27002, C27003 and MVT-601-3201; un-controlled study is TK-AK160108.

For information on the effects of renal or hepatic impairment on the pharmacokinetics of relugolix, see previous section.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

n/a

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable. 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 size of the supportive phase 2 studies (see **Supportive studies** below) relative to the phase 3 study. Plus, results from study C27003 could not be pooled with those from MVT-601-3201 given the different patient populations enrolled in the studies.

2.6.5.6. Supportive study(ies)

The relugolix clinical development program (**Table** 2) includes the following supportive studies: the **phase 2 study C27003**; the **phase 2 study C27002**; and the **phase 1 study TB-AK160108**.

Phase 2 study C27003

Methods

Design: C27003 (NCT02135445; Dearnaley et al. Eur Urol. 2020) is a two-arm, randomized, open label, parallel-group study in patients with localized prostate cancer of intermediate risk and for whom 6 months of neoadjuvant/adjuvant ADT to external beam radiation therapy (EBRT) was indicated. The assessment of appropriate risk for short-term (6 months) ADT was at the discretion of the investigator and/or treating radiation oncologist. Intermediate risk per NCCN guidelines included one of the following: T2b-T2c disease; or Gleason score 7; or PSA 10 to 20 ng/mL. Depending upon physician judgment and as per NCCN guidelines, the presence of more than one intermediate-risk criteria may have been an indication for longer-term ADT, outside the scope of this study.

Patients were randomized (3:2) to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every four weeks for 24 weeks (after a single loading dose of 240 mg) (N = 38).

Objective and endpoints: 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. Castration rate was estimated using a 2-sided 95% confidence interval (CI) and the primary objective was to demonstrate sustained castration in > 90% of patients. Secondary endpoints were testosterone and PSA kinetics, changes in prostate gland size, quality of life, safety, pharmacokinetics, and pharmacodynamics. No formal statistical differences were sought or hypothesized between relugolix and degarelix. The Safety Population, defined as all patients who received at least one dose of any study drug, was used for all efficacy and safety analyses.

Results

Participants: Sixty-five patients in the relugolix group and 38 patients in the degarelix group were included in the Safety Population.

Demographics and other baseline characteristics: Overall, demographics were similar between the treatment groups. The majority of patients were white (89% in the relugolix group, 82% in the degarelix group) and the mean (SD) age of patients was 70.2 (5.65) years in the relugolix group and 70.3 (6.97) years in the degarelix group. Almost all patients in this study were receiving radiotherapy with neoadjuvant/adjuvant ADT as the primary (first line) therapy for their prostate cancer. The mean prostate gland size (SD) was 42005.4 mm^3 (19475.26) in the relugolix group and 50084.8 mm^3 (27974.97) in the degarelix group.

Primary endpoint

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%).

Secondary endpoints

For brevity, the results for the secondary endpoints are not described here. Refer to the Clinical AR for these results.

Phase 2 study C27002

Methods

Design: C27002 (NCT02083185) is a three-arm, randomized, open-label, parallel-group dose-finding study of relugolix in patients with advanced hormone-sensitive prostate cancer, with a leuprolide observational cohort. Relugolix was administered starting with a 320-mg loading dose on Day 1 followed (beginning on Day 2) by a maintenance dose of 80 or 120 mg daily (QD).

This study enrolled adult men with prostate cancer who were candidates for ADT for the management of hormone-sensitive prostate cancer with one of the following clinical disease states: (1) advanced localized disease not suitable for primary therapy, (2) evidence of PSA biochemical or clinical relapse following primary surgery or radiation therapy of curative intent, or (3) newly diagnosed metastatic disease that was asymptomatic or not threatening to vital organs. Patients were randomized 2:2:1 to receive either relugolix (2 dosing groups, see above) or leuprolide.

Objectives and endpoints: The study's primary endpoint was the rate of effective castration between Week 5, Day 1 (Day 29) to Week 25, Day 1 (Day 169) inclusive, defined as the estimated proportion of patients who have testosterone concentrations <50 ng/dL at all scheduled visits. Castration rate was estimated using a 2-sided 95% confidence interval (CI) and the primary objective was to demonstrate sustained castration in > 90% of patients. The secondary endpoints included safety, testosterone and PSA kinetics, pharmacokinetics, pharmacodynamics, and quality of life. No formal statistical differences were sought or hypothesized either between the two relugolix dosing arms or between relugolix and leuprolide. The Safety Population, defined as all patients who received at least one dose of any study drug, was used for all efficacy and safety analyses.

Results

Participants: A total of 134 patients were enrolled into one of three groups to receive oral relugolix for up to 48 weeks at doses of 80 mg (N = 56) or 120 mg (N = 54) orally once daily (after a single oral loading dose of 320 mg), or into a reference control group to receive GnRH receptor agonist therapy (leuprolide, 22.5 mg subcutaneous every 12 weeks, N = 24).

Demographics and other baseline characteristics: Demographics were similar among the treatment groups. The majority of patients were white (80% in the combined relugolix groups, 100% in the leuprolide group). The mean (SD) age of patients was 72.2 (8.64) years in the combined relugolix groups and 68.3 (6.77) years in the leuprolide group. At study entry, ≤ 15% of patients across study groups had evidence of distal metastases (M1 disease), although information on metastatic status was not available for more than 50% of patients in the relugolix groups.

Primary endpoint

Effective castration (testosterone < 50 ng/dL) was achieved and maintained between the Week 5 Day 1 (Day 29) to Week 25 Day 1 (Day 169) visit for each treatment group as follows: relugolix 80 mg group, 91.1% [95% CI: 80.4%, 97.0%]; relugolix 120 mg group, 90.7% [95% CI: 79.7%, 96.9%]; and leuprolide group, 95.8% [95% CI: 78.9%, 99.9%]). The study did not meet the primary endpoint, since the lower bounds of the 95% CIs for both relugolix doses were not > 90%. This outcome is likely driven by the small sample size affecting the statistical power for this assessment.

Secondary endpoints

For brevity, the results for the secondary endpoints are not described here.

Phase 1 study TB-AK1601082

Methods

Design: Study TB-AK160108 (NCT02141659; Suzuki et al. Cancer Med. 2019) is an open-label, dose-range-finding study that evaluated the tolerability, safety, pharmacokinetics and pharmacodynamics of relugolix in 43 hormone treatment-naïve Japanese patients with non-metastatic prostate cancer.

The study consisted of a dose-escalation phase (Part A) and a 96week expansion phase (Part B). In Part A (N = 13), a loading dose of relugolix (320 or 360 mg) was administered on Day 1 followed by once daily oral dosing on Days 2 through 28, with the dosage dependent on tolerability in each individual Cohort of 3 to 4 patients. In Part B, 30 patients received a maximum of 96 weeks of treatment at doses of 80 or 120 mg once daily (N = 15, each group), with a loading dose of 320 mg on Day 1. An overview of the study is show in

Table **26**.

Table 26. Treatment Cohorts for Study TB-AK160108

Cohort	Loading Dose (Day 1)	Maintenance Dose
Part A: Dose-rising phase		
1	320 mg	80 mg QD Days 2 to 28
2	320 mg	120 mg QD Days 2 to 28
3	320 mg	160 mg QD Days 2 to 28
4	360 mg	120 mg QD Days 2 to 28
Part B: Expansion phase		
NA	320 mg	80 mg QD Day 2 to Week 48[a]
NA	320 mg	120 mg QD Day 2 to Week 48[a]

Abbreviations: NA = not applicable; QD = daily.

[a] After completing 48 weeks of treatment, patients were able to continue receiving drug up to a total of 96 weeks, at the discretion of the of the investigator and depending on the wishes of the patient.

Objective and endpoints: The primary objectives of the study were to evaluate the safety and tolerability of relugolix in hormone treatment-naïve patients with non-metastatic prostate cancer. The secondary objectives were to evaluate relugolix pharmacokinetics, its effects on serum testosterone, and the change over time in PSA levels.

Results

Participants: This study enrolled 43 adult Japanese men with prostate cancer who had not yet received hormone therapy. In total, the Full/Safety Analysis Set in Part A of the study comprised 13 patients and in Part B 30 patients (15 in each dosing group, see

Table **26**).

Demographics and other baseline characteristics: The mean age (SD) of the 30 patients in Part B of the study was 74.5 (5.10). All were Japanese and had non-metastatic disease.

Primary endpoint

The results for the safety and tolerability of relugolix are not reported here (see Clinical safety).

Secondary endpoints

In Part A, following the loading dose on Day 1, substantial decreases in mean testosterone concentrations in all cohorts were observed on Day 2. Mean testosterone concentrations were below the 50 ng/dL castration threshold level by Day 3 for Cohorts 1, 2, and 3, and by Day 7 for Cohort 4. Testosterone concentrations of all of the patients, except 1 patient in Cohort 2 who discontinued the study after the first dose, dropped below the 50 ng/dL castration threshold level by Day 2 to Day 14 and continued below this threshold level until Day 31 (i.e., 3 days after the last dose).

In Part B, following the loading dose on Day 1, substantial decreases in mean testosterone concentrations in both groups were observed on Week 1 Day 2 (Day 2). Mean testosterone concentrations were below the 50 ng/dL castration threshold level by Week 1 Day 4 (Day 4), at the latest for both groups. Testosterone concentrations of all of the patients dropped below the 50 ng/dL castration threshold level by Week 1 Day 2 (Day 2) to Week 3 Day 1 (Day 15) and continued below this threshold level until Week 25 Day 1 (Day 169). Testosterone reduction by both doses of relugolix was sustained through 96 weeks.

For brevity, only the results for the secondary endpoint of testosterone suppression are reported here.

2.6.6. Discussion on clinical efficacy

The relugolix clinical development program in prostate cancer consists of the pivotal phase 3 study MVT-601-3201 and the supportive phase 2 studies C27003 and C27002, plus the phase 1 study TB-AK160108. This clinical development program appears generally acceptable.

Design and conduct of clinical studies

Pivotal study. The design of study **MVT-601-3201** was in general considered acceptable at SA (EMA/CHMP/SAWP/742698/2015) and this can be agreed.

Patient population. The patients enrolled in the pivotal study were not candidates for surgical or radiation therapy with curative intent. The eligibility criteria of study MVT-601-3201 are in general considered acceptable, except for the following.

At SA it was considered that including subgroups of patients with 1) evidence of biochemical (PSA) or clinical relapse following primary intervention with curative intent; and 2) newly diagnosed androgen sensitive metastatic disease, seems appropriate for the definition of the population according to the aimed therapeutic indication. However, at SA there was a point of critique on also including a subgroup of patients with 3) advanced localized disease unlikely to be cured by local primary intervention with either surgery or radiation with curative intent. This criterion 3) defines a subpopulation that is different from the other patients allowed in the trial and the rationale for including these patients was not fully understood. Furthermore, the criteria defining unsuitability of locoregional treatment at the time of enrolment appear not to be specified, and they are probably difficult to define in an objective manner. Therefore, the inclusion of subgroup 3) was discouraged because it was expected to confound the interpretation of study results, although mainly in relation to secondary endpoints. It is noted that the Applicant has decided not to follow this part of the SA. It is also noted that, whereas the treatment of patients with continuous ADT per criteria 1) and 2) seems to be in line with current clinical guidelines (2021 EAU Guidelines on prostate cancer; 2020 ESMO Prostate cancer guidelines), for criterion 3) this is considered uncertain. Then again, as the inclusion of subgroup 3) unlikely has any impact on the primary outcome of the study and is also considered of little relevance for the (wording of the) indication, it is acceptable nonetheless.

Patients had to have an ECOG performance status of 0 or 1. This is reflected in section 5.1 of the SmPC.

Relugolix dose selection. The Applicant's rationale for the proposed posology for relugolix is acceptable. The proposed posology was also discussed at the time of SA where the CHMP answered that this posology seemed appropriate to ensure the treatment goal (i.e. > 90% of patients achieving and maintaining medical castration through the end of treatment).

Comparator. At SA, it was remarked that based on the similar mechanism of action, the GnRH antagonist degarelix would be the most obvious comparator. It was, however, acknowledged that the uptake of degarelix in daily practice may have been relatively low due to a number of reasons. Therefore, from a scientific point of view, the leuprolide comparator was acceptable at the time. With regards to the dose and route of administration of leuprolide, it was considered preferable to select a single dose, which should ideally ensure the best compromise between the maximum expected effect on testosterone lowering and safety. Nevertheless, it was acknowledged that the use of different doses seems unavoidable in a global trial setting. However, it was considered imperative to demonstrate that there are no efficacy differences across the various leuprolide dose regimens at the time of registration.

At present, the uptake in clinical practice of the GnRH antagonist degarelix has not changed importantly since at the time of SA. Leuprolide is (still) a recommended, standard of care treatment

option and its use as a comparator is thus acceptable. The results of the subgroup analysis of the different leuprolide dose levels will be viewed with special interest.

Primary endpoint. At the time of SA, the Applicant proposed as the primary endpoint of the study the probability of testosterone ≤ 50 ng/dL while on study treatment from Week 5 Day 1 through Week 48 Day 7, which seems to correspond to Evaluation Criterion 1 (see Table 9). The CHMP considered this primary endpoint acceptable.

In chapter 2 of Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man that contains condition-specific guidance on prostate cancer (EMA/CHMP/703715/2012 Rev. 2), the following is stated in the section on therapy for metastatic disease (hormone-naïve). For medicinal products aiming at achieving medical castration, it is sufficient to convincingly demonstrate the achievement and maintenance of castrate levels of testosterone in the absence of breakthroughs and micro-surges. It is also stated that if the aim is to achieve "surgical level" of castration, 20 ng/dL and below, clinical benefit should be demonstrated in a randomized trial vs. standard therapy (target 50 ng/dL and below) if the benefit of a lower serum testosterone target level cannot be demonstrated by other means.

Moreover, already in 2007 the following was concluded by the CHMP in the Vantas Article 29(4) referral procedure (CHMP/247760/07, see Annex II): the achievement of castrate levels of testosterone (serum testosterone < 50 ng/dL) is an acceptable primary efficacy endpoint in patients with hormone sensitive advanced prostate cancer. Vantas is an implant containing the GnRH agonist histrelin acetate.

When taking the above in account, it thus seems that Evaluation Criterion 1 could also be considered the regulatory requirement for the EMA and it is uncertain why the Applicant assumes otherwise. It is, however, noted that the primary endpoint is of pharmacodynamic nature and is not a clinical measure of patient benefit *per se*.

The -10% non-inferiority margin is acceptable, primarily as it is based on regulatory precedence of the pivotal assessment of the GnRH receptor antagonist degarelix versus leuprolide (Firmagon MAA EPAR). At SA, no specific remarks on the -10% non-inferiority margin were made.

Secondary endpoints. At SA, the proposed secondary endpoints were considered acceptable. It is noted though, that apart from the (key) secondary endpoint of castration resistance-free survival (CRFS) all alpha-protected secondary endpoints that were tested hierarchically are of pharmacodynamic nature or concern a biomarker (PSA as a surrogate endpoint), and are not clinical measures of patient benefit *per se*. It is also noted that the quality of life endpoints are not alpha-protected and not for hierarchical testing. Lastly, it is noted that at the time of SA the proposed study design included an optional extension treatment period of an additional 48 weeks (for both treatment arms). This extension treatment period was apparently later dropped, as it was not/no longer included in the original study protocol (dated 13-Jan-2017).

Statistical methods. Study MVT-601--3201 enrolled a total of 3 cohorts of patients and both a primary and a final analysis were conducted. The primary analysis included the results of patients from Cohort 1 only and these are considered key for benefit-risk assessment. The sample size (calculation) of 915 treated patients at the primary analysis (in Cohort 1) was considered adequate at SA. The choice to use the results of Cohort 1 and Cohort 2 (additional patients with metastatic disease) is acceptable. With protocol Amendment 3 the Applicant chose to enrich the study with metastatic patients for the secondary endpoint of CRFS (to be analysed at the final analysis) due to an assumed higher incidence of castration resistance (PSA progression) in patients with metastatic disease. This can be understood- and is acceptable, also as CRFS is a rather 'low-ranked' secondary endpoint (see Table 10). Results of the efficacy analysis in the China cohort (Cohort 3) were not included in the

primary analysis CSR and are therefore not included in this assessment report, and thus not discussed here.

The 2:1 randomization ratio is acceptable, but given the trial is open-label, there was a risk of (early) dropout/censoring in the leuprolide (control) arm, which will preclude the observation of some events in this arm. Reassuringly, there was very little early dropout/censoring in the leuprolide (control) arm (see Figure 13).

The three stratification factors, i.e. geographic region; presence of metastatic disease; and age, are acceptable. As the dose of leuprolide in Japan, Taiwan, and China is 11.25 mg instead of the 22.5 mg in other countries, the stratification factor geographic region is considered an important one. See also above at **Comparator.** Apart from this, no major prognostic effect of all three stratification factors is expected on the pharmacodynamic outcomes of the study, including the primary endpoint.

In light of the different administration routes of relugolix (oral) and leuprolide (SC or IM injection), the open-label study design is acceptable. The Applicant provided a detailed description of the data access restrictions that were put in place for study MVT-601-3201 to minimize bias and protect trial integrity in the context of an open-label trial. Based on the information provided, it is noted that the blinded team consisted of a statistician in charge of writing the SAP and a programmer. The rest of the study team was unblinded. In this context, and despite the level of restrictions described by the Applicant, it is difficult to exclude any data-driven decisions once the study was ongoing. In particular, it is noted that all functions other than biostatistics involved in the development of the SAP were unblinded at the time of its late finalisation.

All analysis populations can be acceptable. The use of the mITT population as the primary population for efficacy endpoints, i.e. excluding patients who were randomized but not treated, is acceptable as only two patients in each treatment group were excluded (see Figure 13).

At the time of SA the CHMP considered the statistical methods based on the Kaplan-Meier analysis adequate to evaluate the relugolix efficacy using the cumulative probability of sustained testosterone suppression. The associated predefined decision rules were considered adequate as well. The proposed censoring mechanisms and the imputation rules applied to the intent-to-treat population were endorsed. It was advised that sensitivity analyses needed to be clearly pre-specified in the protocol (not provided at the time) including a per-protocol analysis and different censoring rules. Generally this advice was followed. Censoring rules deviate somewhat from the advice, they are somewhat simplified but are still considered reasonable, the main difference is in the handling of relugolix and leuprolide adherence. Since the compliance was generally high, this is not of concern. Sensitivity analyses were specified in the SAP. Although their description is rather short, they do test main assumptions of the primary analysis model and are agreed. Some inconsistency is, however, noted between the protocol and the SAP regarding the censoring rules. The brief protocol description states that subjects who discontinue treatment prior to observing an event will be "*censored at the last testosterone assessment prior to discontinuation*", whereas the SAP describes that "*patients who discontinued from the study prior to Week 5 Day 1 will be censored at the target day of Week 5 Day 1*". The Applicant explained that the censoring rule for patients who discontinued treatment prior to Week 5 Day 1 was updated based on feedback received by the FDA. A sensitivity analysis was provided based on the per-protocol description, i.e. with patients censored at the last testosterone assessment prior to discontinuation, and the results of this sensitivity analysis were consistent with the primary analysis.

The performed subgroup analyses, including for the two different dose levels (22.5 mg vs 11.25 mg) in the leuprolide group, are acceptable.

At the time of SA, the sequential scheme for both superiority and non-inferiority primary comparisons and for the secondary endpoints was considered valid to control the overall type I error rate. The

methods for the statistical analysis of the secondary endpoints proposed by the Applicant (at the time) were considered adequate. This still is the case. Of note, no hypotheses were pre-specified in the protocol or SAP for the secondary endpoints. However, it was assumed that these were standard superiority hypotheses.

Study conduct. Regarding the additional analyses performed after the database lock for the primary analysis, the following remarks are made. It is noted that additional analyses of cardiovascular safety were conducted post hoc. The Applicant states that a safety analysis of adverse cardiovascular events, including MACE and ischemic heart disease, was prespecified for study MVT-601--3201 (see-Clinical safety). However, no such analysis is mentioned in the protocol. In the SAP, the AE category of adverse cardiovascular events that includes both MACE and ischemic heart disease *is* mentioned, but no specific statistical safety analysis is indicated, nor is any safety analysis included in the hierarchical testing order (Table 10). At SA the Applicant proposed rate of MACE as a secondary endpoint and the CHMP at the time suggested that risk factors for cardiovascular events were to be assessed at baseline and concomitant medications reported in order to avoid imbalances in the analysis of MACE and allow proper interpretation of the results. For further discussion on this matter, refer to Discussion on clinical safety.

The (three) amendments to the protocol are unlikely to have (had) a major impact on the study results (especially of the primary analysis that is considered key for benefit-risk assessment) or the scientific validity of the study. They could, therefore, be acceptable. Then again, several important changes to the statistical methods were done as part of protocol Amendment 3 (addition of key secondary endpoint, additional metastatic patient cohort, distinction between primary and final analyses). In addition, the first SAP, which provides details of the fixed-sequence testing procedure and all planned analyses, was only effective when the primary analysis data were near complete (and several revisions were made subsequently). Due to the open-label nature of the study, data driven decisions cannot be ruled out. Therefore, the Applicant was requested to comment on the impact of the protocol amendments and of the late SAP finalisation/revisions on the trial integrity and overall control of the type I error, especially for the key secondary endpoints. According to the Applicant, the decisions to add new endpoints and the ordering of the secondary endpoints in the fixed-sequence testing procedure were based on the review of historical data. In addition, it is argued that the study data blinding plan ensures the study integrity and the overall control of the type I error. It was understood that FDA comments on the SAP resulted in subsequent revisions. However, as discussed above, the blinded team consisted of the statistician writing the SAP and a programmer only, and the rest of the study team was unblinded. Despite other data access restrictions, it is difficult to completely rule out any data-driven decisions in the context of an open-label study. More specifically, the late ranking of the confirmatory secondary endpoints in the SAP could be of concern, leading to a potential inflation of the study type I error. This is an issue that cannot be addressed retrospectively, so it will not be pursued further. Plus, although undesirable, this issue does not concern the primary endpoint of the study and it is thus not considered key for B/R assessment.

The overall rate of important protocol deviations (**IPDs**) of 21.9% could be considered rather high, but the following remarks are made.

There were amongst others IPDs due to administrative issues and IPDs due to patients receiving prohibited concomitant medications. For these the (results of) the performed sensitivity and subgroup analyses should provide reassurance. Moreover, a sensitivity analysis was performed using the per protocol population excluding all patients with IPDs.

Other IPDs were due to the sponsor not communicating to investigators non-castrate levels (on or after Week 5 Day 1 [Day 29]) that were detected centrally by the more sensitive liquid chromatography-tandem mass spectrometry method. According to the Applicant, these IPDs did not

have either an urgent or actual impact on patient safety or on the scientific validity of the study. Primarily, as according to the Applicant investigators had enough resources available to them to make actual treatment decisions for study patients in line with best clinical practice and professional guidelines. This is acceptable. Investigators did have available PSA levels at every visit and total testosterone levels (measured per standard assays) at Week 5, Week 25, and Week 49. This is considered sufficient, as it is in line with current guideline recommendations for the follow-up of men on ADT (2021 EAU Guidelines on prostate cancer). Moreover, it is standard clinical practice that a rising PSA prompts the assessment of the testosterone level and this was available to be drawn at any unscheduled visit per the investigator's discretion. This was the case for more patients in the leuprolide group than in the relugolix group. However, the observed difference can be explained by the delay in achieving testosterone suppression in patients in the leuprolide group compared with the relugolix group, i.e. the fact that testosterone suppression occurs later with leuprolide treatment compared with relugolix treatment.

All in all, it is considered unlikely that the IPDs had a significant impact on the study results or the scientific validity of the study. Plus, the results of the performed sensitivity and subgroup analyses should provide reassurance.

Efficacy data and additional analyses

Recruitment. It is noted that that 29.6% of patients assessed for eligibility failed screening, primarily due to not meeting eligibility criteria. This could suggest that the eligibility criteria, in particular the exclusion criteria, were rather strict.

Approximately 90% of patients in both study arms completed the 48 weeks of treatment. The ~10% of patients who discontinued/withdrew from the study early, primarily due to AEs or withdrawal by patient (70% of patients who discontinued), is acceptable.

Baseline demographic and disease-specific characteristics. Patient demographics and disease specific baseline characteristics were in general similar between treatment groups in study MVT-6013201. Any (small) differences observed are unlikely of influence on the study results, especially on the primary endpoint. Moreover, these patient characteristics can be considered representative of the intended target population. No major differences seem apparent- between the primary analysis patient population and the -mITT- Final Analysis Population (or the mITT Metastatic Patient Population) that were used for analysis of the rather 'low-ranked' (see Table 10), key secondary CRFS endpoints only.

Subgroup 3) of patients with advanced localized disease unlikely to be cured by local primary intervention with either surgery or radiation with curative intent, the subgroup of which inclusion was discouraged at SA, comprised 27.1% of patients.

The reported prior and concomitant medical therapies that could alter testosterone levels are considered of no/unlikely influence on the study results, especially on the primary endpoint. Regarding the influence on the PSA endpoints of the reported concomitant medical therapies that could possibly affect or alter PSA, any advantage of the relugolix group over the leuprolide group for the key secondary PSA endpoint can be excluded. Plus, the results of the sensitivity analyses should provide reassurance regarding all prior and concomitant medical therapies that could alter testosterone or PSA levels. Regarding prior and concomitant radiation therapy, this does not affect testosterone levels, and therefore, is not expected to impact the primary endpoint. Moreover, the influence on the key secondary PSA endpoint of the three patients in the relugolix group who started radiotherapy to the prostate bed less than 2 months after study initiation is considered minimal.

Primary endpoint - sustained castration rate.

Primary analysis. The study successfully met its primary endpoint of sustained castration rate based on both evaluation criteria. Treatment with relugolix thus resulted in sustained testosterone suppression below castrate levels (< 50 ng/dL) and treatment with relugolix was non-inferior to treatment with leuprolide. According to the Applicant, the between-group difference demonstrated not only non-inferiority of relugolix to leuprolide, but also statistical superiority, as the lower bound of the 95% CI was > 0, with p < 0.0001). This interpretation is not supported. Whereas it is considered that non-inferiority of relugolix to leuprolide has, indeed, been demonstrated, superiority of relugolix over leuprolide has not. If superiority was to be claimed, it should have been included in the testing hierarchy. In the current testing strategy, the type 1 error is propagated to the next secondary endpoint, if it is also propagated to a superiority test on sustained castration rate of relugolix compared to leuprolide, the overall type 1 error rate is no longer protected.

It should be noted that the observed sustained castration rate of 88.8% in the leuprolide group is substantially lower than the protocol assumption of 96% (used for sample size determination). This 96% assumed sustained castration rate for leuprolide stems from the phase 3 degarelix registration study, which showed a 96.4% (95% CI: 92.5, 98.2) probability of sustained castration for the leuprolide group (from Day 28 to Day 364; Firmagon MAA EPAR). In contrast, the observed sustained castration rate of 96.7% for the relugolix group *is* in line with the protocol assumption of 94%. In the absence of another reasonable explanation for a different comparator response rate, the difference in leuprolide formulation between the two studies, i.e. leuprolide 3-month depot injections vs. monthly Lupron® (leuprolide) 7.5 mg, respectively might be considered as a potential factor of the discrepancy. This uncertainty on the response level of the leuprolide arm in study MVT-601-3201, possibly related to the formulation, should be carefully considered in the interpretation of the efficacy results.

Sensitivity analyses. Sensitivity Analyses 1 and 2 provided reassurance that the IPDs and patients receiving concomitant medications and herbal supplements that could possibly affect testosterone did not have a significant impact on the results of the primary endpoint. It is noted that although Sensitivity Analysis 3 did meet Evaluation Criterion 2 (non-inferiority to leuprolide), the lower bound of the 95% CI for the relugolix group was less than 90% and Evaluation Criterion 1 was thus not met. This is acceptable, as Sensitivity Analysis 3 (counting patients who had missed two or more consecutive visits after Week 5 Day 1 or discontinued from the study early as having an event) is considered a rather conservative analysis. Sensitivity Analysis 4 corrected for (censored) patients who had not reached castrate levels of testosterone at Week 5 Day 1 (17 in leuprolide and four in relugolix). The results of this sensitivity analysis were consistent with the results from the primary analysis, providing reassurance that the results of the primary endpoint were not impacted by the somewhat delayed effect of leuprolide on testosterone suppression in some patients.

In conclusion, the results of the sensitivity analyses are considered to support the robustness of the primary efficacy analysis. Results from three of the four sensitivity analyses were consistent with the primary analysis of the primary endpoint in terms of the lower bound of the 95% CI for sustained castration rate exceeding the 90% threshold in the relugolix group (Evaluation Criterion 1). Per the rather conservative Sensitivity Analysis 3, the results were generally consistent with the primary analysis but did not meet Evaluation Criterion 1. All four sensitivity analyses demonstrated non-inferiority of relugolix compared with leuprolide (Evaluation Criterion 2).

Subgroup analyses. In virtually all subgroups, the result confirmed the results of the primary analysis of the primary endpoint, both for Evaluation Criterion 1 and 2. These subgroup analyses are thus considered to support the robustness of the primary efficacy analysis. Regarding the subgroup analysis of the different leuprolide dose levels, it is noted that the large majority of patients in the leuprolide group received leuprolide at the 25 mg dose level, i.e. 86% (264/308) of patients vs 14% (44/308) of patients who received leuprolide at the 11.25 mg dose level. All 44 patients who received leuprolide at the 11.25 mg dose level were from Japan, Taiwan, and China. It is also noted that the lower leuprolide

dose level in these patients does not seem to negatively impact efficacy, i.e. does not result in a lower cumulative probability of sustained castration. This is considered reassuring for the comparison of the relugolix group with the whole leuprolide group.

Secondary endpoints. Except for time to testosterone recovery, all key secondary endpoints tested at the primary analysis in hierarchical order (see Table 10) demonstrated superiority over leuprolide in a statistically significant manner. Treatment with relugolix thus: a) achieved testosterone suppression rapidly, more rapidly than treatment with leuprolide; b) resulted in a PSA response more rapidly than treatment with leuprolide; c) achieved profound testosterone suppression (< 20 ng/dL) more rapidly than treatment with leuprolide; and d) resulted in a greater degree of FSH suppression (at Week 25 Day 1) than treatment with leuprolide.

At the final analysis, treatment with relugolix did not result in an improvement of castration resistance free survival (during the 48-week treatment) over treatment with leuprolide in patients with metastatic prostate cancer (mITT Metastatic Patient Population). As a result, the subsequent key secondary endpoints in the hierarchical testing order (including time to testosterone recovery) were not formally tested/were merely analysed as exploratory.

Still, the cumulative incidence rate of testosterone recovery to > 280 ng/dL at 90 days after drug discontinuation was numerically higher in the relugolix group compared with the leuprolide group and there was thus a trend for a shorter time to/faster testosterone recovery after study drug discontinuation for the relugolix group compared with the leuprolide group.

For brevity, the results of the other (non-key) secondary endpoints, that were not part of the hierarchical testing order, and of the exploratory endpoint overall survival are not discussed as these are considered to have little impact on/to be of little value for the benefit-risk assessment. Only the following two remarks are made.

Regarding patient-reported outcomes/quality of life, a numerically lower score for the EORTCQLQPR25 hormonal treatment-related symptoms domain was observed at the 90-day follow up visit. The value of this isolated finding is considered uncertain, but could have a relation with the observed trend for a shorter time to/faster testosterone recovery after study drug discontinuation for the relugolix group compared with the leuprolide group.

Regarding overall survival, there were few deaths during study MVT-601-3201 and follow-up (after the study and before database lock) and the vast majority of these were due to a treatment-emergent AE.

Special populations. The number of patients in the pivotal study aged ≤ 75 or > 75 years old is shown in

Table 12 (specified per treatment group). Table 25 shows the numbers of patients in all specified age categories > 65 years old across the relugolix prostate cancer program studies.

Supportive studies.

Study C27703. The patient population enrolled in this study C27003 is different from the patient population of the pivotal phase 3 study MVT-601-3201. Whereas the pivotal study enrolled patients with advanced prostate cancer who were mostly treated without curative intent/in a palliative setting, almost all patients in study C27003 were receiving radiotherapy with neoadjuvant/adjuvant ADT as the primary (first-line) therapy for their prostate and all were treated with curative intent. This is, however, not considered to have any impact on (the results of) the primary endpoint in both studies.

Importantly, study treatment was in line with current European clinical guidelines, as among the treatment recommendations for patients with intermediate-risk prostate cancer (who are suitable for ADT) there in is combined intensity modulated radiotherapy with short term ADT (4 to 6 months; 2021 EAU Guidelines on prostate cancer).

It is noted that relugolix dosing in study C27003 was slightly different from the pivotal phase 3 study MVT-601-3201.

Study C27003 met its primary endpoint of rate of sustained castration, but it is noted that formal statistical testing was not conducted. The (thus also) merely descriptive results of the secondary endpoints testosterone and PSA kinetics are in line with what could be expected when comparing an oral formulation of a GnRH receptor antagonist with an injectable 1-month depot formulation, based on their identical mechanism of action but differing pharmacokinetics.

In conclusion, notwithstanding the slightly different relugolix dosing used in study C27003 and the fact that formal statistical testing was not conducted, the results from this study can be considered to provide some support for the activity of relugolix in lowering testosterone to castration levels in a sustainable manner, in patients with hormone-sensitive prostate cancer (in this study being patients with localized intermediate-risk disease).

Study C27702. The patient population enrolled in study C27002 is similar to the patient population of the pivotal phase 3 study MVT-601-3201. Also, in study C27002 patients with advanced localized disease not suitable for primary therapy could be enrolled, besides patients with evidence of biochemical or clinical relapse following treatment with curative intent and patients with newly diagnosed metastatic disease. The remarks made above regarding this subgroup "3)" in the main study also apply here.

It is noted that relugolix dosing in study C27002 was different from in the pivotal phase 3 study MVT-601-3201.

It is also noted that study C27002 did not meet its primary endpoint of rate of sustained castration, since the lower bounds of the 95% CIs for both relugolix doses were not > 90%. The Applicant argues that this outcome is likely driven by the small sample size affecting the statistical power for this assessment. It is uncertain whether this is truly the case, but this will not be further discussed or pursued, also as formal statistical testing was not conducted. The (thus also) merely descriptive results of the secondary endpoints testosterone and PSA kinetics are in line with what could be expected when comparing an GnRH receptor antagonists with a receptor agonists, based on their respective mechanism of action.

In conclusion, notwithstanding the different relugolix dosing used in study C27002 and the fact that the study did not meet its primary objective of sustained castration, the results from this dose-finding

study can be considered to provide some support for the activity of relugolix in lowering testosterone to castration levels in a sustainable manner, in patients with hormone-sensitive prostate cancer.

Study TB-AK160108. Naturally, the support from this small phase 1 dose range-finding study for the efficacy of relugolix is limited. Plus, it is noted that (unsurprisingly) relugolix dosing in study TB-AK160108 was different from in the pivotal phase 3 study MVT-601-3201. Nevertheless, the results from the dose range-finding study TB-AK160108 can also be considered to provide some support for the activity of relugolix in lowering testosterone to castration levels in a sustainable manner, in patients with hormone-sensitive prostate cancer.

Originally, the Applicant proposed an indication for the treatment of **advanced prostate cancer**. It is, however, noted that only patients with androgen-sensitive advanced prostate cancer were enrolled in study MVT-601-3201, and this should be adequately reflected in the indication. Moreover, the proposed indication is very similar to the approved indication of the GnRH antagonist Firmagon (degarelix), i.e.- "*FIRMAGON is a gonadotrophin releasing hormone (GnRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer.*" (see Firmagon SmPC). It is, however, important to note that the CHMP for this wording of the Firmagon indication took into account that in the pivotal study for Firmagon, non-inferiority to leuprolide control had been investigated using biological criteria only and not clinical endpoints indicative of a direct benefit (see Firmagon MAA EPAR). The same is true for the pivotal relugolix study MVT-601-3201, as the primary endpoint and all secondary endpoints that were tested statistically are of pharmacodynamic nature or concern a biomarker, and are not clinical measures of patient benefit *per se* (see above). All in all, it is considered that the wording of the Orgovyx (relugolix) indication should also include the words "*advanced* ***hormone--sensitive*** *prostate cancer*", in line with other, more recent approvals in this disease setting (see Xtandi SmPC, Erleada SmPC, and Zytiga SmPC).

Plus, in 2019 the EMA developed a paper to strengthen consistency when defining (the wording of) therapeutic indications in the product information of medicines (EMA/CHMP/483022/2019). Based on this guidance, the Applicant removed the pharmacotherapeutic class ("*is a gonadotropin-releasing hormone (GnRH) receptor antagonist*") from the wording. In light of this guidance, it could also be considered to request the Applicant to add "*as monotherapy*" to the indication, since relugolix was investigated in the pivotal study as such. However, for patients with newly diagnosed, metastatic hormone-sensitive prostate cancer, i.e. one of the three 'advanced prostate cancer' patient subgroups in the pivotal study, ADT monotherapy is no longer considered standard of care. Current clinical guidelines recommend a combination of ADT with docetaxel, abiraterone, enzalutamide, or apalutamide (or radiotherapy; 2021 EAU Guidelines on prostate cancer; 2020 ESMO Prostate cancer guidelines). An approval with a restrictive monotherapy indication would severely limit/hamper the use of relugolix for treating these patients in clinical practice with such combination therapy. Of note, some patients in the pivotal study did receive combination treatment of relugolix with docetaxel (n=8) or enzalutamide (n=17), for some time during the study. Refer to ***Baseline data*** - **Prior and concomitant medical therapies that could alter testosterone or PSA levels**. It is, however, uncertain whether the concomitant use of relugolix and docetaxel, abiraterone, enzalutamide, or apalutamide will have any relevant (detrimental) effect on relugolix efficacy and/or safety. For reassurance, the Applicant provided PK and PD data/results for 20 patients in study MVT-601-3201 who received combination treatment with enzalutamide and relugolix. No clinical meaningful differences in the PK of relugolix or in testosterone suppression were observed in these 20 patients, see section Pharmacokinetics. In addition, the Applicant referred to the ongoing phase 1 safety and tolerability study MVT-601-049 investigating the combination of relugolix with either abiraterone, apalutamide, or docetaxel with respect to PK and PD (NCT04666129). The Applicant is recommended to submit the final CSR as a post-authorisation measure (PAM) in 4Q of 2023 (see also section Discussion on clinical pharmacology).

2.6.7. Conclusions on the clinical efficacy

In the pivotal study MVT-601-3201 patients with androgen sensitive advanced prostate cancer were randomized to treatment with either the oral GnRH antagonist relugolix or standard-of-care depot injections of the GnRH agonist leuprolide. The study met its primary endpoint, as treatment with relugolix resulted in a sustained castration rate of ≥ 90%, i.e. a testosterone level < 50 ng/dL from Day 29 through 337 (Evaluation Criterion 1), plus treatment with relugolix was noninferior to treatment with leuprolide as assessed by sustained testosterone suppression rate (Evaluation Criterion 2). The results of the sensitivity and subgroup analyses are considered to support the robustness of the primary efficacy analysis of the primary endpoint. All key secondary endpoints tested hierarchically at the primary analysis, except for (time to) testosterone recovery, demonstrated superiority over or at least confirmed noninferiority to leuprolide. Although both primary and all key secondary endpoints that were tested statistically are of pharmacodynamic nature or concern a biomarker, achievement of castrate levels of testosterone is an acceptable primary efficacy endpoint in patients with hormone sensitive advanced prostate cancer and is considered to meet the CHMP regulatory requirements.

The initially applied indication was amended to reflect the pivotal study population, i.e. only patients with androgen-sensitive advanced prostate cancer, and be aligned with relevant precedents (Firmagon, Xtandi, Erleada, and Zytiga). Further, the data/results from study MVT-601-3201 are not considered sufficient proof of patient benefit beyond the hormone-sensitive prostate cancer setting. Plus, any indication beyond the hormone-sensitive prostate cancer setting would not be in line with EMA guidance and regulatory precedents.

2.6.8. Clinical safety

Main safety information for oral relugolix 120 mg once daily following a single dose of 360 mg loading dose in the treatment of patients with advanced prostate cancer is based on the pivotal phase 3 study MVT-601-3201. The GnRH agonist leuprolide was used as active control in this study. Leuprolide was given as a 3-month depot injection, every 12 weeks for 48 weeks (last injection occurred 12 weeks prior to the end of the treatment period).

Results of safety analyses from the final analysis population, including the safety analyses for the subgroup of patients with metastatic disease, are considered supportive data.

In addition, supportive safety data is derived from three other studies in prostate cancer:

- C27002: phase 2 study of relugolix in patients with advanced prostate cancer (similar population to that for MVT-601-3201); controlled by the GnRH agonist leuprolide
- C27003: phase 2 study of relugolix as neoadjuvant/adjuvant to external beam radiotherapy in localized prostate cancer patients; controlled by the GnRH antagonist degarelix
- TB-AK160108: phase 1 dose-range-finding study of relugolix in prostate cancer patients eligible for ADT.

Additional safety data were collected from 13 clinical pharmacology studies in healthy participants and participants with hepatic or renal failure.

Further, clinical studies with relugolix monotherapy 40 mg in women with uterine fibroids or endometriosis are included. Given the lower dose used, the different indication, and different demographics, use of data is limited to the evaluation of adverse events of clinical interest (alanine

aminotransferase [ALT] or aspartate aminotransferase [AST] ≥ 3 × the upper limit of normal [ULN]), as drug-induced liver injury is often idiopathic and dose independent.

These studies provide safety data on 2495 patients exposed to relugolix (935 patients with prostate cancer, 1004 women with uterine fibroids or endometriosis, and 556 participants in clinical pharmacology studies).

2.6.8.1. Patient exposure

Prostate Cancer Indication

The pivotal phase 3 study MVT-601-3201 is considered the primary analysis population for evaluation of the safety of relugolix 120 mg once daily in advanced prostate cancer patients. There were two analyses for this study: a primary analysis and a final analysis.

- The primary analysis of safety occurred after 934 patients were randomized to the study (Cohort 1) and completed the 48-week treatment period and 30-day safety follow-up visit or discontinued early.
- The final analysis of the study occurred after 434 patients with metastatic disease (of whom 295 patients were also included in the primary analysis [Cohort 1]) were randomized to the study (Cohort 1 and Cohort 2) and completed the 48-week treatment period and 30-day safety follow-up visit or discontinued early. The study remains ongoing. To support registration in China, additional patients are being enrolled in the study from China and Taiwan (under Protocol Amendment 3). In total there were 18 patients with metastatic disease from either China (7 patients) or Taiwan (11 patients) included in the final analysis as they were randomized prior to the completion of the enrollment of patients supporting the final analysis (ie, enrolled by 31 Jul 2019).

The number of patients included in each analysis set of **pivotal phase 3 study MVT-601---3201** is presented in Table 27.

Table 27. Number of Patients in Each Analysis Population by Treatment Group (All Randomized Patients)

Primary Patient Population (dbl 10 Dec 2019)	Relugolix (N = 624)	Leuprolide (N = 310)	Total (N = 934)
Primary Safety Population	622 (99.7%)	308 (99.4%)	930 (99.6%)
Final Patient Population (dbl 23 Sep 2020)	Relugolix (N = 719)	Leuprolide (N = 359)	Total (N = 1078)
Final Analysis Safety Population	717 (99.7%)	357 (99.4%)	1074 (99.6%)
Metastatic Patient Safety Population	290 (40.3%)	144 (40.1%)	434 (40.3%)

Abbreviations: mITT = modified intent-to-treat; N = number of patients in the treatment group.
Percentages are based on the total number of patients in all randomized patients for each treatment group or total.
Note: Four patients who did not receive study drug (two patients in each treatment group.

A summary of exposure to study drug and compliance in the Primary Analysis Safety Population of pivotal phase 3 study MVT-601-3201, which is the main safety analysis, is presented in

Table **28**:

Table 28. Extent of Exposure and Compliance, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

	Relugolix (N = 622)	Leuprolide (N = 308)	Total (N = 930)
Treatment duration (weeks)[a]			
N	622	308	930
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
Treatment duration category (weeks), n (%)			
≤ 4 weeks	5 (0.8%)	1 (0.3%)	6 (0.6%)
> 4 to ≤ 12 weeks	12 (1.9%)	2 (0.6%)	14 (1.5%)
> 12 to ≤ 24 weeks	10 (1.6%)	7 (2.3%)	17 (1.8%)
> 24 to ≤ 36 weeks	21 (3.4%)	11 (3.6%)	32 (3.4%)
> 36 to ≤ 48 weeks	305 (49.0%)	77 (25.0%)	382 (41.1%)
> 48 weeks	269 (43.2%)	210 (68.2%)	479 (51.5%)
Compliance[b]			
N	622	308	930
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
Compliance, n (%)[b]			
< 80%	1 (0.2%)	0	1 (0.1%)
≥ 80% to ≤ 100%	449 (72.2%)	249 (80.8%)	698 (75.1%)
> 100%	172 (27.7%)	59 (19.2%)	231 (24.8%)

Abbreviations: Max = maximum; Min = minimum; N = number of patients in the treatment group; n = number of patients included in summary statistics; QD = once daily; 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 administrated / (treatment duration in weeks / 12)] / 22.5 mg or 11.25 mg per treatment on Day 1) × 100.
Source: Table 7.1.7.1, MVT-601-3201 Primary Analysis CSR.

Note: Concomitant treatments allowed to counteract adverse effects of androgen-deprivation

Concomitant treatments were allowed to prevent disease exacerbation due to flare-up in the leuprorelin treatment arm. Patients were permitted to take antiandrogen therapies including, but not limited to, bicalutamide during the study for the prevention of the initial flare response in the leuprolide group for the first 4 weeks or longer. Antiandrogen therapies including, but not limited to, enzalutamide were also allowed in both groups after the confirmation of PSA progression as defined by the PCWG3 criteria (Scher et al. 2016) or other disease progression in the setting of testosterone suppression to castrate levels. Antiandrogen therapies were otherwise prohibited on study.

The use of concomitant bone-modifying agents to prevent BMD loss during clinical studies was at the discretion of the treating investigator.

Supportive Women's Health Studies

In the Women's Health 12-Week Monotherapy Safety Population, 1311 female patients were exposed to at least one dose of relugolix (ranging from 10 to 40 mg) from eight pooled studies of women with uterine fibroids or endometriosis.

Clinical Pharmacology Studies

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).

2.6.8.2. Adverse events

Summary of adverse events

MVT-601-3201

An overall summary of adverse events for the primary analysis of study MVT-601-3201 is presented in Table 29.

Table 29. Overall Summary of Adverse Events in Study MVT-601-3201 (Primary Analysis Safety Population)

Patients with at Least One AE, n (%)	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%)

The database lock date for the primary analysis 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. 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 7.3.1.1, MVT-601-3201 Primary Analysis CSR.

The overall incidence of AEs in the primary analysis of study MVT-601-3201 was similar for the two treatment groups. No obvious difference in the incidence of AEs between relugolix and leuprorelin was found, except for withdrawal due to the different route of administration (relugolix via daily oral tablet versus leuprolide by 3-month depot subcutaneous injection).

C27002

An overall summary of adverse events in study C27002 is presented by treatment group in

Table 30.

Table 30. Overview of Adverse Events, Study C27002, Safety Population

Patients with at Least One AE, n (%)	Relugolix 80 mg QD (N = 56)	Relugolix 120 mg QD (N = 54)	Leuprorelin Q12W (N = 24)
Any AE	53 (94.6%)	50 (92.6%)	23 (95.8%)
Leading to study treatment discontinuation	2 (3.6%)	2 (3.7%)	0
Leading to study treatment dose modification	6 (10.7%)	8 (14.8%)	0
Grade 3 or above	5 (8.9%)	4 (7.4%)	2 (8.3%)
Grade 3 or above related to study drug	2 (3.6%)	1 (1.9%)	1 (4.2%)
Related to study drug	45 (80.4%)	45 (83.3%)	18 (75.0%)
Serious	6 (10.7%)	2 (3.7%)	2 (8.3%)
Serious and related to study drug	0	1 (1.9%)	0
Serious and leading to study treatment discontinuation	1 (1.8%)	0	0
Fatal outcome	1 (1.8%)	0	1 (4.2%)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; Q12W = every 12 weeks; QD = once daily; SAE = serious adverse event.
Notes: Percentages are based on the total number of patients in the Safety Population in each column.
Patient Incidence: A patient was counted only once for each category.
Source: Table 4.1.2, Study C27002.

C27003

An overall summary of adverse events in study C27003 is presented by treatment group in Table 31.

Table 31. Overview of Adverse Events, Study C27003, Safety Population

Patients with at Least One AE, n (%)	Relugolix 120 mg QD (N = 65)	Degarelix 80 mg Q4W (N = 38)
Any AE	56 (86)	37 (97)
Grade 3 or higher AE	1 (2)	4 (11)
Drug-related AE	50 (77)	28 (74)
Drug-related Grade 3 or Higher AE	0	1 (3)
SAE	1 (2)	3 (8)
Drug-related SAE	0	0
AE resulting in study drug discontinuation	0	0
AE resulting in study drug dose modification	2 (3)	0
Death	0	0

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; Q4W = every 4 weeks; QD = once daily; SAE = serious adverse event.
Notes: Percentages are based on the total number of patients in the Safety Population in each column.
Patient Incidence: A patient was counted only once for each category.
Source: Table 12.d, CSR C27003.

TB-AK160108

The phase 1 dose-finding study TB-AK160108 (80, 120, 160 mg QD) in 16 patients did not show an obvious dose dependency. However, the numbers on patients were too small to draw firm conclusions.

Common adverse events

Primary safety analysis MVT-601-3201

A summary of AEs reported for at least 5% of patients (per preferred term) for the primary analysis of study MVT-601-3201 is presented in Table 32.

Table 32. Summary of Adverse Events Reported for ≥ 5% of Patients in Either Treatment Group by Preferred Term in Study MVT-601-3201 (Primary Analysis 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 for the primary analysis was 10 Dec 2019.
Abbreviations: AE = adverse event; 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 7.3.1.3, MVT-601-3201 Primary Analysis CSR.

AEs were generally reported with similar incidence between the two treatment groups with exception events associated with MACE, and adverse events of constipation, diarrhoea, arthralgia, and hypertension. Observed differences were usually small, and did not follow a trend or pattern.

The most commonly reported (> 10% patients) AEs in any treatment group included hot flush, fatigue, constipation, diarrhoea, arthralgia, and hypertension.

All constipation and diarrhoea AEs were mild or moderate (grade 1 or grade 2) in severity. There were no serious adverse events (SAEs) of constipation or diarrhoea. One patient in the relugolix group was withdrawn from the study due to a nonserious grade 2 AE of constipation. Most arthralgia AEs were mild or moderate (grade 1 or grade 2) in severity, and none were serious or led to study drug interruption or withdrawal.

Constipation, diarrhoea, and musculoskeletal pain (which includes arthralgia) are included in Section 4.8 of the proposed SmPC for relugolix as 'very common' adverse drug reactions ADRs).

Study C27002

AEs reported for ≥ 10% of patients in study C27002 are presented for each treatment group by preferred term in Table 33.

Table 33. Adverse Events Report for ≥ 10% of Patients in Any Treatment Group by Decreasing Frequency of Preferred Term, Study C27002, Safety Population

Preferred Term	Relugolix 80 mg QD (N = 56)	Relugolix 120 mg QD (N = 54)	Leuprorelin Q12W (N = 24)
Patients with at least one adverse event, n (%)	53 (94.6)	50 (92.6)	23 (95.8)
Hot flush	31 (55.4)	35 (64.8)	15 (62.5)
Fatigue	11 (19.6)	17 (31.5)	7 (29.2)
Cataract	5 (8.9)	11 (20.4)	0
Alanine aminotransferase increased	6 (10.7)	3 (5.6)	4 (16.7)
Aspartate aminotransferase increased	5 (8.9)	1 (1.9)	3 (12.5)
Pollakiuria	1 (1.8)	0	3 (12.5)
Hyperhidrosis	2 (3.6)	0	3 (12.5)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; Q12W = every 12 weeks; QD = once daily.
Notes: Percentages are based on the total number of patients in the Safety Population in each column.
AEs were coded using MedDRA Version 18.0.
Patient Incidence: A patient was counted once for each preferred term with any incidence of the event.
Source: Table 4.2.2, Study C27002.

Cataracts were observed and reported as AEs in both relugolix groups compared to no patients in the leuprolide group. This is attributed to enhanced surveillance as the protocol-specified use of slit lamp examinations in the relugolix groups only. Slit lamp examinations (visual acuity) were conducted as part of monitoring for phospholipidosis (PLD). The median age of the patients was 73 years. The observed incidence is generally consistent with the epidemiology of cataract development.

Study C27003

AEs reported for ≥ 10% of patients in study C27003 are presented for each treatment group by preferred term in Table 34.

Table 34. Adverse Events Report for ≥ 10% of Patients in Either Treatment Group by Decreasing Frequency of Preferred Term, Study C27003, Safety Population

Preferred Term	Relugolix 120 mg QD (N = 65)	Degarelix 80 mg Q4W (N = 38)
Patients with at least one adverse event, n (%)	56 (86)	37 (97)
Hot flush	37 (57)	23 (61)
Fatigue	17 (26)	6 (16)
Diarrhoea	12 (18)	5 (13)
Cataract	10 (15)	7 (18)
Nocturia	9 (14)	5 (13)
Pollakiuria	8 (12)	6 (16)
Dysuria	5 (8)	6 (16)
Blood testosterone increased	2 (3)	4 (11)
Urine flow decreased	1 (2)	4 (11)
Alanine aminotransferase increased	0	5 (13)
Injection site erythema	0	4 (11)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; Q4W = every 4 weeks; QD = once daily.
Notes: Percentages are based on the total number of patients in the Safety Population in each column.
AEs were coded using MedDRA Version 18.0.
Patient Incidence: A patient was counted once for each preferred term with any incidence of the event.
Source: Table 12.f, CSR C27003.

TB-AK160108

The most commonly reported AE was hot flush. No new or unexpected safety findings were found, also due to the very small groups.

Adverse Events Related to Study Treatment

Primary analysis MVT-601-3201

A summary of AEs reported for ≥ 5% of patients (per preferred term) in the Primary Analysis Safety Population is presented by relationship to study drug, as evaluated by the investigator, in

Table 35.

Table 35. Drug-Related Adverse Events Reported in at Least 5% of Patients in Either Treatment Group by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

Preferred Term	Relugolix 120 mg QD (N = 622)	Leuprolide (N = 308)
Patients with at least one drug-related AE, n (%)	458 (73.6%)	212 (68.8%)
Hot flush	337 (54.2%)	159 (51.6%)
Fatigue	118 (19.0%)	52 (16.9%)
Weight increased	40 (6.4%)	20 (6.5%)
Asthenia	25 (4.0%)	16 (5.2%)
Hypertension	18 (2.9%)	19 (6.2%)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; QD = once daily.
Related AEs were rated by the investigators as possibly or probably related to study drug.
Patients with multiple events for a given preferred term were 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 7.3.1.5, MVT-601-3201 Primary Analysis CSR.

Drug-related AEs were reported slightly more in the relugolix group, however the proportion was in the same range (73.6%) and the leuprolide group (68.8%). The AEs were expected for treatments that lower testosterone levels (hot flush, fatigue, weight increased, asthenia, hypertension).

C27002

AEs related to study drug and reported for ≥ 10% of patients in study C27002 are presented by preferred term for each treatment group in Table 36.

Table 36. Drug-Related Adverse Events Reported for ≥ 10% of Patients in Any Treatment Group by Preferred Term, Study C27002, Safety Population

Preferred Term	Relugolix 80 mg QD (N = 56)	Relugolix 120 mg QD (N = 54)	Leuprorelin Q12W (N = 24)
Patients with at least one Drug-related AE, n (%)	45 (80.4)	46 (85.2)	18 (75.0)
Hot flush	30 (53.6)	33 (61.1)	13 (54.2)
Fatigue	10 (17.9)	16 (29.6)	6 (25.0)
Alanine aminotransferase increased	7 (12.5)	3 (5.6)	3 (12.5)
Aspartate aminotransferase increased	6 (10.7)	1 (1.9)	2 (8.3)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; Q12W = every 12 weeks; QD = once daily; SOC = system organ class.
Notes: Percentages are based on the total number of patients in the Safety Population in each column.
AEs were coded using MedDRA Version 18.0. AEs were graded according to version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events.
Patient Incidence: A patient was counted once for each preferred term with any incidence of the event.
Source: Table 4.6.1, Study C27002.

The proportion of patients in each treatment group with drug-related events was comparable or slightly higher (80-mg 80.4%, 120-mg 85.2% and 75.0% for leuprorelin). Most frequent events hot flush and fatigue are expected adverse reactions with the use of androgen deprivation therapy (ADT). ALT and AST increased are listed for ADT products.

C27003

AEs related to study drug and reported for ≥ 10% of patients in study C27003 are presented by preferred term for each treatment group in Table 37.

Table 37. Drug-Related Adverse Events Reported for ≥10% of Patients in Any Treatment Group by Preferred Term, Study C27003, Safety Population

Preferred Term	Relugolix 120 mg QD (N = 65)	Degarelix 80 mg Q4W (N = 38)
Patients with at least 1 drug-related AE, n (%)	50 (77)	28 (74)
Hot flush	36 (55)	20 (53)
Fatigue	15 (23)	5 (13)
Injection site erythema	0	4 (11)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of subjects in the treatment group; n = number of patients with specified AE; Q4W = every 4 weeks; QD = once daily
Notes: Percentages are based on the total number of patients in the Safety Population in each column.
AEs were coded using MedDRA Version 18.0.
Patient Incidence: A patient was counted once for each preferred term with any incidence of the event.
Source: Table 12.h, CSR C27003.

A similar proportion of patients in each treatment group had AEs related to study drug (77% of patients for relugolix and 74% of patients for degarelix), with as most common events hot flush. Fatigue occurred more frequently on relugolix (23% vs 13%). Injection site reactions were obviously only reported for degarelix.

Adverse Events Grade 3 or Higher

Primary Analysis MVT-601-3201

Grade 3 or higher adverse events reported for ≥ 0.5% of patients in any group by preferred term in the Primary Analysis Safety Population are presented below:

Table 38. Grade 3 or Higher Adverse Events Reported in at Least 0.5% of Patients in Either Treatment Group by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

Preferred Term	Relugolix 120 mg QD (N = 622)	Leuprolide (N = 308)
Patients with at least one grade ≥ 3 AE, n (%)	112 (18.0%)	63 (20.5%)
Hypertension	10 (1.6%)	2 (0.6%)
Diabetes mellitus	6 (1.0%)	2 (0.6%)
Syncope	6 (1.0%)	3 (1.0%)
Acute myocardial infarction	5 (0.8%)	1 (0.3%)
Acute kidney injury	4 (0.6%)	1 (0.3%)
Cataract	4 (0.6%)	1 (0.3%)
Hot flush	4 (0.6%)	0
Urinary tract infection	4 (0.6%)	1 (0.3%)
Back pain	2 (0.3%)	3 (1.0%)
Prostate cancer metastatic	2 (0.3%)	2 (0.6%)
Gamma-glutamyltransferase increased	1 (0.2%)	2 (0.6%)
Blood alkaline phosphatase increased	0	2 (0.6%)
Cardio-respiratory arrest	0	3 (1.0%)
Cerebral haemorrhage	0	2 (0.6%)
Dysphagia	0	2 (0.6%)
Inguinal hernia	0	3 (1.0%)
Neutropenia	0	2 (0.6%)
Type 2 diabetes mellitus	0	3 (1.0%)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; QD = once daily.
Adverse event grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.
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 7.3.2.2, MVT-601-3201 Primary Analysis CSR.

The most frequently reported (≥ 1% of patients) grade ≥ 3 AEs in any treatment group included hypertension, diabetes mellitus, syncope, back pain, cardiorespiratory arrest, inguinal hernia, and type 2 diabetes mellitus. Grade ≥ 3 AEs of hypertension were reported in a higher proportion of patients in the relugolix group (1.6%) than the leuprolide group (0.6%).

Study C27002

Grade 3 or higher AEs in study C27002 are summarized by treatment group and decreasing preferred term in

Table 39.

Table 39. Grade 3 or Higher Adverse Events by Preferred Term, Study C27002, Safety Population

Preferred Term	Relugolix 80 mg QD (N = 56)	Relugolix 120 mg QD (N = 54)	Leuprorelin Q12W (N = 24)
Patients with at least one Grade 3 or higher AE, n (%)	5 (8.9)	4 (7.4)	2 (8.3)
Alanine aminotransferase increased	1 (1.8)	0	0
Arthralgia	0	1 (1.9)	0
Aspartate aminotransferase increased	1 (1.8)	0	0
Bladder cancer	1 (1.8)	0	0
Cerebral haemorrhage	1 (1.8)	0	0
Cervical vertebral fracture	1 (1.8)	0	0
Gamma-glutamyltransferase increased	1 (1.8)	0	0
Hypercalcaemia	0	1 (1.9)	0
Hypertension	0	1 (1.9)	0
Hypotension	1 (1.8)	0	0
Incision site pain	0	1 (1.9)	0
Inguinal hernia	0	1 (1.9)	0
Musculoskeletal pain	0	1 (1.9)	0
Syncope	0	1 (1.9)	0
Diabetes mellitus	0	0	1 (4.2)
Myocardial infarction	0	0	1 (4.2)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; Q12W = every 12 weeks; QD = once daily; SOC = system organ class.
Notes: Percentages are based on the total number of patients in the Safety Population in each column.
AEs were coded using MedDRA Version 18.0. AEs were graded according to version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events.
Patient Incidence: A patient was counted once for each preferred term with any incidence of the event.
Source: Table 4.9.1, Study C27002.

The overall incidence of grade 3 or higher AEs over 48-weeks of treatment was similar between the relugolix (8.2% of patients [80-mg 8.9% and 120-mg 7.4%]) and leuprorelin groups (8.3% of patients).

Study C27003

Grade 3 or higher AEs in study C27003 are summarized by treatment group and decreasing preferred term in

Table 40.

Table 40. Grade 3 or Higher Adverse Events by Preferred Term, Study C27003, Safety Population

Preferred Term	Relugolix 120 mg QD (N = 65)	Degarelix 80 mg Q4W (N = 38)
Patients with at least one Grade 3 or higher AE, n (%)	1 (2)	4 (11)
Paranasal sinus hematoma	0	1 (3)
Pleural effusion	0	1 (3)
Esophagitis ulcerative	0	1 (3)
Pulmonary contusion	0	1 (3)
Ankle fracture	0	1 (3)
Fibula fracture	0	1 (3)
Radius fracture	0	1 (3)
Ulna fracture	0	1 (3)
Road traffic accident	0	1 (3)
Facial bones fracture	0	1 (3)
Jaw fracture	0	1 (3)
Rib fracture	0	1 (3)
Diabetes mellitus	0	1 (3)
Mesothelioma malignant	0	1 (3)
Headache	1 (2)[a]	0
Cold sweat	0	1 (3)
Hypertension	1 (2)[a]	0

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; Q4W = every 4 weeks; QD = once daily; SOC = system organ class.
Notes: Percentages are based on the total number of patients in the Safety Population in each column.
AEs were coded using MedDRA Version 18.0. AEs were graded according to version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events.
Patient Incidence: A patient was counted once for each preferred term, high level term, and SOC with any incidence of the event.
[a] These events occurred in a single patient.
Source: Table 12.g, CSR C27003.

The overall incidence of grade 3 or higher AEs was lower in the relugolix group compared to the degarelix group (2% vs. 11%). The two grade 3 or higher events (headache and hypertension) were reported for the same patient in the relugolix group and these events were reported as serious AEs, assessed as not related to study drug by the investigator, and did not lead to treatment discontinuation.

Study TB-AK160108

In Part A, 1 of 3 patients in Cohort 1 (relugolix 80 mg) had a grade 3 or higher AE of hypertension, which was not considered to be drug-related and, therefore, not a dose limiting toxicity. No other grade 3 or higher AEs were reported in Part A.

In Part B, 10 patients (5/15 patients in each treatment group) were reported to have a grade 3 or higher AE. An AE of grade 3 or higher hypertension was reported for 2/15 patients in the relugolix 80-mg group and an additional patient was reported to have blood pressure increased, for a combined total of three patients in the relugolix 80-mg group for this complex of related terms; all other grade 3 or higher AE in either relugolix group were reported for one patient each.

2.6.8.3. Serious adverse event/deaths/other significant events

Primary analysis MVT-601-3201

A summary of SAEs reported for ≥ 0.5% of patients by preferred term is presented for the Primary Analysis Safety Population in Table 41.

Table 41. Serious Adverse Events Reported for ≥ 0.5% of Patients in Either Treatment Group by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

Preferred Term	Relugolix 120 mg QD (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; N = number of patients in the treatment group; n = number of patients with specified AE; QD = once daily.
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 7.3.3.2, MVT-601-3201 Primary Analysis CSR.

A total of 123 patients had a SAE. The incidence of SAEs was lower for the relugolix group (12.2%; 76 patients) compared with the leuprolide group (15.3%; 47 patients).

Drug-relationship: Drug-related SAEs were reported in both groups (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 haemorrhage, 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 with drug-related SAEs were cardiac failure, sinus node dysfunction, and hyperglycaemia and transient ischemic attack (both in a single patient). No drug-related SAE was reported for more than one patient.

Severity: Eighty-one patients (8.7%) had a SAE that was a grade 3 maximum severity, 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 SAE: 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 SAE: liver function test abnormal in one patient, pulmonary oedema and rhabdomyolysis in another patient.

C27002

SAEs were reported in 6 patients (10.7%) in the relugolix 80-mg group, 2 patients (3.7%) in the relugolix 120-mg group, and 2 patients (8.3%) in the leuprorelin group. No SAE was reported in more than 1 patient in any group. One SAE, embolic stroke in a patient in the relugolix 120-mg group, was assessed by the reporter to be drug-related.

C27003

In study C27003, SAEs were reported for a lower proportion of patients in the relugolix group compared with the degarelix group (2% [one patient; headache and hypertension] vs. 8% [three patients; esophagitis ulcerative, road traffic accident and mesothelioma malignant with pleural effusion], respectively).

TB-AK160108

No SAEs were reported for patients in Part A. In Part B, 6 patients (3/15 patients in each dose group) had one or more SAEs, All SAEs were reported in only one patient in either dose group. The SAE of cerebral infarction was considered drug-related and led to study drug discontinuation and the outcome of the SAE was reported as recovering/resolving at the end of the study.

Deaths

Sixteen deaths were reported in study MVT-601-3201 at the time of the primary analysis (7 ([1.1%] in the relugolix group and 9 [2.9%] in the leuprolide group) and five deaths (4 relugolix, 1 leuprolide) were reported in study C27002. Subsequently, at the time of the MVT-601-3201 final analysis, deaths had been reported in 10 patients (1.4%) in the relugolix group and 11 patients (3.1%) in the leuprolide group. In the final analysis of study MVT-601-3201, five additional patients (three relugolix, two leuprolide) died (relugolix group acute respiratory failure, death [suspect metastatic prostate cancer], and myocardial infarction; leuprolide group: COVID-19 pneumonia and prostate cancer).

All cases were assessed by the investigator as not related to study drug, with the exception of one fatal case that was considered possibly related: a 74-year old patient on relugolix for 138 days had a fatal acute myocardial infarction.

The 27 deaths reported during the safety reporting period of studies MVT-601-3201 and C27002, and also the death for one patient who died after the adverse event reporting period are listed in

Table 42.

Table 42. Listing of Deaths

Study	Age (years)/ Race	Oral Daily Dose (mg)	Duration of Exposure (Days)	Event with Fatal Outcome	Start Day/ End Day[a]	Relationship to Study Drug
MVT-601-3201 Relugolix	68/White	120	332	Myocardial infarction	343/343	Not Related
	74/White	120	138	Acute myocardial infarction	139/140	Possible
	74/White	120	61	Non-small cell lung cancer metastatic	86/97	Not Related
	80/White	120	270	Acute respiratory failure	290/294	Not related
	69/White	120	333	Unknown/Sudden deterioration of patient's health	Outside the reporting period	Not Related
	70/White	120	229	Prostate cancer	113/234	Not Related
	87/White	120	218	Prostate cancer metastatic	219/244	Not Related
	74/White	120	280	Small cell lung cancer metastatic	259/347	Not Related
	71/White	120	25	Death	36/36	Not Related
	74/Not reported	120	51	Acute kidney injury	38/75	Not Related
	71/White	120	6	Myocardial infarction	7/7	Not Related
C27002 Relugolix	70/White	80	129	Cerebral haemorrhage	131/131	No
	89/White	80	674	Cardiac arrest	683/683	No
	85/White	120	422	Sudden death	444/444	No
	81/White	120	424	Death	431/431	No
MVT-601-3201 Leuprolide	70/White	22.5	248	Prostate cancer metastatic	345/428	Not Related
	81/White	22.5	1	Cardiac failure congestive Aortic stenosis	19/64 22/64	Not Related Not Related
	83/White	22.5	171	Cardiopulmonary failure and Epistaxis	172/172 171/172	Not Related
	84/Asian	11.25	1	Cardio-respiratory arrest and Multiple organ dysfunction syndrome	67/68	Not Related
	68/White	22.5	85	Cerebral haemorrhage	132/136	Not Related
	66/ Black or African American	22.5	85	Homicide	168/168	Not Related
	72/Asian	22.5	85	COVID-19 pneumonia	260/290	Not Related
	86/White	22.5	253	Cardio-respiratory arrest	352/352	Not Related
	76/White	22.5	1	Cardio-respiratory arrest	8/8	Not Related
	76/White	22.5	85	Prostate cancer	147/147	Not Related
	67/White	22.5	85	Prostate cancer metastatic	132/138	Not Related
C27002 Leuprolide	71/White	22.5	90	Myocardial infarction	158/158	No

Abbreviations: CSR = clinical study report; ID = identification; IM = intramuscular; SC = subcutaneous
[a] Start/end day is relative to the date of first dose of study drug in days.
MedDRA Version 22.0.
Source: Table 39, Listing 16.2.4.1, Listing 16.2.5.1, Listing 16.2.7.5 MVT-601-3201 Final Analysis CSR; Table 12.h, Listing 16.2.7.1, Listing 16.2.5.1, Listing 16.2.4.1 C27002 CSR.

Adverse events of special interest

Safety parameters of clinical interest represent prespecified categories of adverse events that are either:

- **known toxicities of ADT with GnRH receptor agonists**:
    - carbohydrate and lipid metabolic effects,
    - adverse cardiovascular events,
    - loss of bone mineral density,
    - QTc prolongation,
    - mood disorders,
    - and vasomotor symptoms
- **potential risks associated with relugolix based on nonclinical data**
    - hepatic transaminase elevations
- **theoretical risks with an investigational agent**
    - hypersensitivity

An overall summary of AEs in these categories is presented in Table 43 for the Primary Analysis Safety Population of the Pivotal Phase 3 Study MVT-601-3201.

Table 43. Summary of Adverse Event Categories of Interest in Descending Order of Frequency for the Relugolix Group, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

AE Categories of Clinical Interest	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 for the primary analysis was 10 Dec 2019.
Abbreviations: AE = adverse event; 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 7.3.8.1, MVT-601-3201 Primary Analysis CSR.

Vasomotor symptoms

Vasomotor symptoms (mainly hot flush, but also hyperhidrosis, feeling hot, night sweats, and flushing) are known AEs of androgen deprivation therapy with GnRH receptor agonists. As can be expected, all studies showed vasomotor symptoms in approximately 50-60% of patients and incidence was comparable between relugolix and leuprolide, and relugolix and degarelix.

Carbohydrate and lipid metabolic effects: Glucose metabolism

The resulting adverse events are summarized by preferred term for the Primary Analysis Safety Population in

Table 44.

Table 44. Adverse Events Related to Glucose Metabolism by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

Preferred Term	Relugolix 120 mg QD (N = 622)	Leuprolide (N = 308)
Patients with at least one AE related to hyperglycemia or diabetes, n (%)	36 (5.8%)	19 (6.2%)
Diabetes mellitus	23 (3.7%)	6 (1.9%)
Hyperglycaemia	5 (0.8%)	6 (1.9%)
Blood glucose increased	3 (0.5%)	1 (0.3%)
Type 2 diabetes mellitus	3 (0.5%)	6 (1.9%)
Glycosylated haemoglobin increased	2 (0.3%)	0
Diabetes mellitus inadequate control	1 (0.2%)	0
Glucose tolerance impaired	0	1 (0.3%)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified adverse event; QD = once daily; SMQ = standardised MedDRA Query.
Search criteria Hyperglycemia/New Onset Diabetes Mellitus SMQ (narrow).
Patients with multiple events for a given preferred term were 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 7.3.8.5, MVT-601-3201 Primary Analysis CSR; Table 4.35.2.

AEs related to abnormal glucose metabolism were reported in both relugolix (5.8%) and leuprolide (6.2%) groups in the pivotal phase 3 study. 'Diabetes mellitus' was reported with a higher incidence on relugolix (3.7%) compared to leuprolide (1.9%); however, for ' type 2 diabetes mellitus' this was lower with relugolix compared to leuprolide (0.5% and 1.9%, respectively). Most events of diabetes mellitus were exacerbations of existing diabetes. In time, mean glucose concentrations increased with an overall mean increase at Week 49 of 0.39 mmol/L on relugolix and 0.51 mmol/L on leuprolide.

As also for the final analysis and the other prostate cancer studies, there was no trends in AE terms relating to glucose metabolism:

C27002

Shifts in glucose levels from baseline grade 0 to grade 2 occurred for 21% of patients in the relugolix 80-mg group and 23% of patients in the relugolix 120-mg group, compared with 9% of patients in the leuprorelin group. However, no differences in HbA1c were observed.

C27003

In study C27003, there were no clear imbalances in AE terms relating to glucose metabolism. Shifts in glucose levels from baseline grade 0 to grade 2 occurred for two patients (3%) in the relugolix group and one patient (3%) in the degarelix group, and one patient in the relugolix group (2%) had a shift from baseline grade 0 to grade 3. Overall changes in median and mean values of HbA1c were minor, with median increases from 0.1% to 0.3%. There were some upward shifts of HbA1c in diabetic patients who had elevated HbA1c at baseline.

TB-AK160108

There were no clear trends in AE terms relating to glucose metabolism during study TB-AK160108. In Part B, 2/15 patients in the relugolix 120 mg group were reported to have AEs of diabetes mellitus and both events were considered drug related. Neither patient had an event assessed as grade 3 or higher, serious, or resulting in study drug discontinuation. No clinically significant changes from baseline were noted in HbA1c levels over the course of the study in either the relugolix 80 mg or 120 mg group.

Carbohydrate and lipid metabolic effects: Lipid metabolism

The resulting adverse events are summarized by preferred term for the Primary Analysis Safety Population in

Table 45.

Table 45. Adverse Events Related to Lipid Metabolic Effects by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

Preferred Term	Relugolix 120 mg QD (N = 622)	Leuprolide (N = 308)
Patients with at least one AE of dyslipidaemia, n (%)	19 (3.1%)	7 (2.3%)
Blood cholesterol increased	4 (0.6%)	0
Blood triglycerides increased	4 (0.6%)	0
Hypertriglyceridaemia	4 (0.6%)	5 (1.6%)
Hypercholesterolaemia	3 (0.5%)	2 (0.6%)
Hyperlipidaemia	3 (0.5%)	0
Dyslipidaemia	2 (0.3%)	0

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified adverse event; QD = once daily; SMQ = standardised MedDRA Query.
Search criteria included Dyslipidaemia SMQ (broad).
Patients with multiple events for a given preferred term were 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 7.3.8.5, MVT-601-3201 Primary Analysis CSR and Table 4.36.2.

In the pivotal phase 3 study, AEs related to abnormal lipid metabolism were similar in both groups (3.1% in the relugolix group and 2.3% in the leuprolide group). Individual events (including blood cholesterol increased, blood triglycerides increased, hypertriglyceridemia, dyslipidaemia, hypercholesterolemia, and hyperlipidaemia) did not occur >1%, except hypertriglyceridaemia in the leuprolide group (1.6%). Results in the final analysis were comparable to results reported for the Primary Analysis. No obvious differences in lipid metabolism were observed between groups over 48 weeks of treatment.

C27002

In study C27002 there were no clear imbalances in AE terms relating to lipid metabolism. Mean values of lipids were generally stable over time with only slight increases in LDL cholesterol without differences between treatment groups.

C27003

In study C27003 there were no clear imbalances in AE terms relating to lipid metabolism. Mean values of lipids were generally stable over time with only slight increases in LDL cholesterol without differences between treatment groups.

TB-AK160108

In study TB-AK160108 there were no clear trends in AEs relating lipid metabolism. No clinically significant changes from baseline were noted in serum lipid levels over the course of the study in either the relugolix 80 mg or 120 mg group.

Hepatic Transaminase Elevations

In the primary analysis of study MVT-601-3201, there were 13 patients with an AE of clinical interest (ALT and/or AST ≥ 3× ULN) reported during the study: 9 (1.4%) on relugolix and 4 (1.3%) on leuprolide. The proportion of patients with laboratory values meeting predefined limits of change at any time for ALT or AST were similar in both treatment groups. One SAE of grade 4 liver function test abnormal was reported for a patient with widely metastatic disease in the leuprolide group; no action was taken with study drug leuprolide (this is also not possible as this is a 3-month depot formulation). One patient on relugolix discontinued study drug due to alanine aminotransferase increased.

General liver safety AEs were searched for using the Drug-Related Hepatic Disorders SMQ (narrow); the resulting AEs are summarized by preferred term for the Primary Analysis Safety Population in

Table 46.

Table 46. Adverse Events per the Drug-Related Hepatic Disorders SMQ by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

Preferred Term	Relugolix 120 mg QD (N = 622)	Leuprolide (N = 308)
Patients with at least one AE of hepatic transaminase elevation, n (%)	47 (7.6%)	17 (5.5%)
Alanine aminotransferase increased	26 (4.2%)	8 (2.6%)
Aspartate aminotransferase increased	17 (2.7%)	4 (1.3%)
Gamma-glutamyltransferase increased	14 (2.3%)	7 (2.3%)
Hepatic function abnormal	3 (0.5%)	0
Liver disorder	2 (0.3%)	0
Transaminases increased	2 (0.3%)	0
Hepatic enzyme increased	1 (0.2%)	0
Hepatic steatosis	1 (0.2%)	0
Hypertransaminasaemia	1 (0.2%)	0
Prothrombin time prolonged	1 (0.2%)	0
Hyperbilirubinaemia	0	1 (0.3%)
Liver function test abnormal	0	1 (0.3%)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n=number of patients with specified AE; QD = once daily; SMQ = standardised MedDRA Query.
Search criteria included Drug-Related Hepatic Disorders SMQ (narrow).
Patients with multiple events for a given preferred term were 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 7.3.8.4, CSR MVT-601-3201.

The proportion of patients with laboratory values meeting predefined limits of change at any time for ALT or AST were also similar in both treatment groups (

Table 47). There were no patients with bilirubin increase of > 2 × ULN in either the relugolix or leuprolide groups. No patient had either ALT and/or AST ≥ 3 × ULN and total bilirubin > 2 × ULN with

or without alkaline phosphatase < 2 × ULN (ie, there were no events meeting the definition of Hy's law).

Table 47. Summary of Changes in ALT, AST, and Bilirubin Values Meeting Predefined Limits of Change at Any Time (Primary Analysis Safety Population)

	Relugolix (N = 622)	Leuprolide (N = 308)	Total (N = 930)
Liver Function[a]			
ALT > ULN and < 3× ULN	168 (27.0%)	83 (26.9%)	251 (27.0%)
ALT ≥ 3× ULN and < 5× ULN	4 (0.6%)	4 (1.3%)	8 (0.9%)
ALT ≥ 5× ULN and < 10× ULN	2 (0.3%)	0	2 (0.2%)
ALT ≥ 10× ULN and < 20× ULN	0	0	0
ALT ≥ 20× ULN	0	0	0
AST > ULN and < 3× ULN	112 (18.0%)	60 (19.5%)	172 (18.5%)
AST ≥ 3× ULN and < 5× ULN	4 (0.6%)	0	4 (0.4%)
AST ≥ 5× ULN and < 10× ULN	0	1 (0.3%)	1 (0.1%)
AST ≥ 10× ULN and < 20× ULN	0	0	0
AST ≥ 20× ULN	0	0	0
ALT or AST > ULN and < 3× ULN	194 (31.2%)	101 (32.8%)	295 (31.7%)
ALT or AST ≥ 3× ULN and < 5× ULN	7 (1.1%)	4 (1.3%)	11 (1.2%)
ALT or AST ≥ 5× ULN and < 10× ULN	2 (0.3%)	1 (0.3%)	3 (0.3%)
ALT or AST ≥ 10× ULN and < 20× ULN	0	0	0
ALT or AST ≥ 20× ULN	0	0	0
Total BILI > ULN	11 (1.8%)(6 1.9%)(17 1.8%)	6 (1.9%)	17 (1.8%)
Total BILI >2× ULN	0	0	0
ALT or AST ≥ 3× ULN and Total BILI > 2× ULN	0	0	0
ALT or AST ≥ 3× ULN and Total BILI > 2× ULN and ALP < 2× ULN	0	0	0

The database lock date for the primary analysis was 10 Dec 2019.
Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; Bili = bilirubin; ULN= upper limit of normal.
[a] Most extreme postbaseline result.
Source: Table 7.3.9.10, MVT-601-3201 Primary Analysis CSR.

Clinical laboratory biochemistry

The overall trends of AST and ALT per visit over time in both relugolix and leuprolide groups were similar.

AEs of clinical interest (ALT and/or AST ≥ 3 × ULN) were reported for nine patients (1.4%) in the relugolix group and for four patients (1.3%) in the leuprolide group. Ten patients (six in the relugolix group; four in the leuprolide group) had ALT ≥ 3 × ULN as shown in the elevation of drug-induced serious hepatotoxicity plot in the dossier.

Supportive prostate cancer studies

In study C27002, hepatic transaminase elevation-related AEs were reported in 11 of 110 patients (10%) in the relugolix groups (7 patients [12.5%] in the 80-mg group and 4 patients [7.4%] in the 120-mg group) and 4 of 24 patients (16.7%) in the leuprorelin group. There were two nonserious events of grade 3 or higher ALT and AST increase, reported in 1 patient in the relugolix 80-mg group. These events did not lead to study drug discontinuation.

In study C27003, no hepatic AEs were reported in the relugolix group. In the degarelix group, 5 patients (13%) were reported to have AEs of ALT increased and 2 patients (5%) were reported to have AEs of AST increased. This imbalance is reflected in the laboratory shift analysis of AST, where shifts in AST from grade 0 to 1 were observed in fewer patients in the relugolix group (3%) than in the degarelix group (16%). There were no events of hepatic transaminase elevation that were grade 3 or higher, serious or led to study drug discontinuation in either group.

In Part A of the study, 1/3 patients in Cohort 1 had an event of an ALT increased, and 1/4 patients in Cohort 3 had an event of hepatic function abnormal. Neither event was serious and neither led to study drug discontinuation.

In Part B, adverse events relevant to hepatic function in 2 or more patients were reported as follows: aspartate aminotransferase increased (4/30 patients), alanine aminotransferase increased (3/30 patients), hepatic function abnormal (3/30 patients), and liver function test increased (2/30 patients). These events were reported for a higher proportion of patients in the relugolix 120 mg group than in the 80 mg group, except for hepatic function abnormal. None of these events were serious or led to discontinuation of study drug.

Clinical Pharmacology Studies in Healthy Participants

In clinical pharmacology studies, 5 of the 556 participants were reported to have transient and reversible hepatic transaminase elevations that met the criterion of an adverse event of clinical interest (≥ 3 × ULN).

Women's Health 12-Week Monotherapy Safety Population

In the Women's Health 12-Week Monotherapy Safety Population, ten AEs of clinical interest were reported. Of these, 7 events (6 in women treated with relugolix [6/1311; 0.2%], 1 in a woman treated with leuprolide [1/223; 0.5%]) were events of ALT ≥ 3 × ULN (data on file). One SAE of liver function test abnormal was reported in a patient with endometriosis from the phase 2 study TAK-385/CCT-001. No events were associated with increased bilirubin. All events resolved.

Hypersensitivity

In the primary analysis of study MVT-601-3201, incidence of AEs related to hypersensitivity were reported for similar proportions of patients in both groups (44 patients [7.1%] in the relugolix group and 26 patients [8.4%] in the leuprolide group), with rash as the most common (3.2% and 2.3% of patients in each group, respectively).

Hypersensitivity is a theoretical risk with a new investigational agent and is therefore investigated. There was no unbalance or trend in the AEs observed that appeared to point to relugolix or to a different pattern with regard to hypersensitivity compared to leuprolide or degarelix.

Therefore, in the proposed prescribing information for relugolix only the standard contraindication has been included ('**Hypersensitivity to the active substance or to any of the excipients**) listed in section 6.1'). However, it is proposed to add 'rash' in the ADR table of section 4.8.

Mood disorders

In the primary analysis of study MVT-601-3201, incidence of AEs related to mood disorders were similar between relugolix and leuprolide (5.1% in the relugolix group and 4.5% in the leuprolide group), consisting of a heterogenous group varying from mood swings to insomnia, but with

depression as the most common (1.9% (n=12) and 1.0% (n=3) of patients in each group, respectively).

Persistently low testosterone with GnRH agonists or antagonists is associated with change in mood disorders. There is no unbalance or trend in the AEs that appears to point to a different pattern with regard to mood disorders compared to leuprolide or degarelix.

Depression is listed in the proposed prescribing information for relugolix (4.8), which is considered appropriate. It is also included in the SmPCs of degarelix (4.8) and leuprolide (4.4, 4.8).

Adverse cardiovascular events

A summary of adverse cardiovascular events and all the components thereof according to the SMQs used for the primary analysis of study MVT-601-3201 is provided in

Table 48.

Table 48. Summary of Adverse Cardiovascular Events (Primary Analysis Safety Population)

No. of patients with at least one AE, n (%)	Relugolix (N = 622)	Leuprolide (N = 308)
Adverse Cardiovascular Events (ie, MACE, IHD, and deaths due to all causes) [a]	24 (3.9%)	22 (7.1%)
MACE [b]	18 (2.9%)	19 (6.2%)
Cardiovascular portion only of MACE [c]	9 (1.4%)	2 (0.6%)
Cerebrovascular portion only of MACE [d]	4 (0.6%)	10 (3.2%)
Deaths due to all causes	7 (1.1%)	9 (2.9%)
MACE in patients with medical history of MACE	3 (3.6%) [e]	8 (17.8%) [e]
MACE in patients without medical history of MACE	15 (2.8%) [f]	11 (4.2%) [f]
Ischemic Heart Disease [g]	15 (2.4%)	5 (1.6%)

The database lock date for the primary analysis was 10 Dec 2019.
Abbreviations: AE = adverse event; IHD = ischemic heart disease; MACE = major cardiovascular adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the treatment group; n = number of patients with specified AE; SMQ = standardised MedDRA Query.
[a] Search criteria included Myocardial Infarction SMQ (broad), Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ (broad), deaths due to all causes, and Ischaemic Heart Disease SMQ (broad).
[b] Search criteria included Myocardial Infarction SMQ (broad), Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ (broad), and deaths due to all causes.
[c] Search criteria included Myocardial infarction SMQ (broad).
[d] Search criteria included Central nervous system haemorrhages and cerebrovascular conditions SMQ (broad).
[e] N = 84 for relugolix and N = 45 for leuprolide (Table 7.3.8.12, MVT-601-3201 Primary Analysis CSR).
[f] N = 538 for relugolix and N = 263 for leuprolide (Table 7.3.8.12, MVT-601-3201 Primary Analysis CSR).
[g] Search criteria included Ischaemic Heart Disease SMQ (broad).
MedDRA Version 22.0.
Source: Table 46, MVT-601-3201 Primary Analysis CSR.

A broad assessment of risk factors for cardiovascular and cerebrovascular events in all patients in the primary analysis was conducted and is presented in Table 49.

Table 49. Summary of Risk Factors (Primary Analysis Safety Population)

	Relugolix (N = 622)	Leuprolide (N = 308)
No. of patients with any risk factors[a]	570 (91.6%)	290 (94.2%)
Life-style related risk factors[b]	422 (67.8%)	202 (65.6%)
Any cerebrovascular or cardiovascular risk factors[c]	488 (78.5%)	254 (82.5%)
Any major adverse cardiac event risk factors history of MACE[d]	84 (13.5%)	45 (14.6%)

The database lock date for the primary analysis was 10 Dec 2019.
Abbreviations: MACE = major cardiovascular adverse event; N = number of patients in the treatment group; SMQ = standardised MedDRA Query.
For all percentages, the denominator is the number of patients in the safety population.
[a] Patients with multiple risk factors were counted only once.
[b] Includes current/past smoker, heavy alcohol use and body mass index > 30.
[c] The risk factors were identified based on a custom medical review.
[d] Search criteria included Myocardial infarction SMQ (broad) and Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ (broad).
Source: Table 7.1.5.4, MVT-601-3201 Primary Analysis CSR.

Post hoc analysis of incidence of MACE

A post hoc analysis of the incidence of MACE events in patients with or without a reported medical history of MACE was performed, applying the MACE query to the medical history data to identify medical history events:

Table 50. Major Adverse Cardiovascular Events with or without a Medical History of a Major Cardiovascular Adverse Event by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

	Relugolix 120 mg QD (N = 622)		Leuprolide (N = 308)	
Preferred Term	Patients with MACE MH (N = 84)	Patients without MACE MH (N = 538)	Patients with MACE MH (N = 45)	Patients without MACE MH (N = 263)
No. of patients with at least one major cardiovascular AE, n (%)	3 (3.6%)	15 (2.8%)	8 (17.8%)	11 (4.2%)
Odds ratio (95% CI) within treatment group (with MACE MH vs without MACE MH)	1.3 (0.4, 4.6)		5.0 (1.9, 13.1)	
Odds ratio (95% CI) between treatment group (leuprolide vs relugolix)			5.8 (1.5, 23.3)	1.5 (0.7, 3.4)
Acute myocardial infarction	0	5 (0.9%)	1 (2.2%)	0
Carotid arteriosclerosis	0	2 (0.4%)	0	0
Ischaemic stroke	0	2 (0.4%)	0	0
Myocardial infarction	1 (1.2%)	1 (0.2%)	0	0
Acute coronary syndrome	0	1 (0.2%)	0	0
Acute kidney injury	0	1 (0.2%)	0	0
Aphasia	0	1 (0.2%)	0	0
Coronary artery occlusion	0	1 (0.2%)	0	0
Electrocardiogram ST segment elevation	0	1 (0.2%)	0	0
Haemorrhagic stroke	1 (1.2%)	0	0	0
Hemiparesis	0	1 (0.2%)	0	0
Lacunar infarction	1 (1.2%)	0	0	0
Non-small cell lung cancer metastatic	0	1 (0.2%)	0	0
Prostate cancer	0	1 (0.2%)	0	0
Prostate cancer metastatic	0	1 (0.2%)	1 (2.2%)	1 (0.4%)
Small cell lung cancer metastatic	1 (1.2%)	0	0	0
Troponin increased	0	1 (0.2%)	0	0

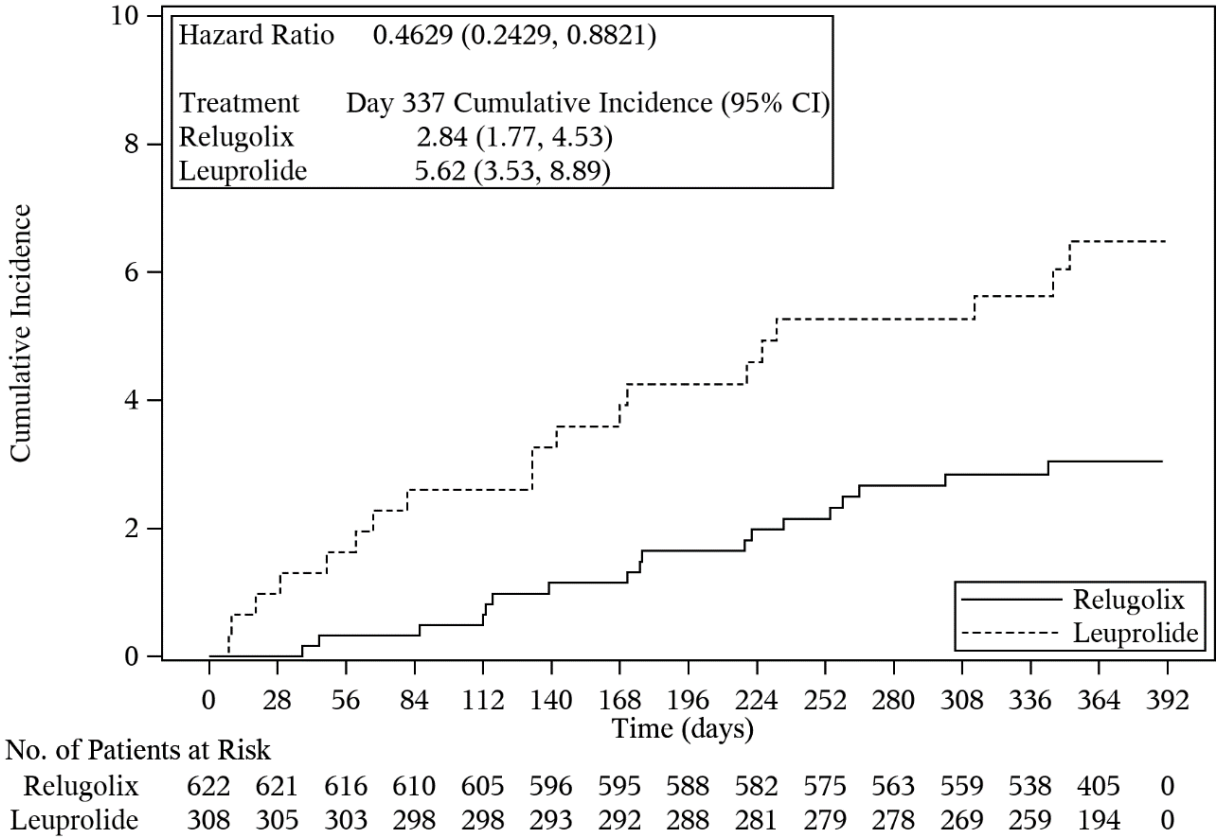
Angina unstable	0	0	0	1 (0.4%)
Aortic stenosis	0	0	0	1 (0.4%)
Cardiac failure congestive	0	0	0	1 (0.4%)
Cardio-respiratory arrest	0	0	2 (4.4%)	1 (0.4%)
Cardiopulmonary failure	0	0	0	1 (0.4%)
Carotid artery occlusion	0	0	0	1 (0.4%)
Cerebral haemorrhage	0	0	1 (2.2%)	1 (0.4%)
Cerebrovascular accident	0	0	1 (2.2%)	0
Cerebrovascular insufficiency	0	0	0	1 (0.4%)
Dysarthria	0	0	1 (2.2%)	0
Epistaxis	0	0	0	1 (0.4%)
Haemorrhage intracranial	0	0	0	1 (0.4%)
Homicide	0	0	1 (2.2%)	0
Multiple organ dysfunction syndrome	0	0	1 (2.2%)	0
Transient ischaemic attack	0	0	2 (4.4%)	2 (0.8%)

Abbreviations: AE = adverse event; CSR = clinical study report; MACE = major adverse cardiovascular event; MH = medical history; N = number of patients in the treatment group; n = number of patients with specified AE; QD = once daily; SMQ = standardised MedDRA Query.
Search criteria included Myocardial Infarction SMQ (broad), Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ (broad), and deaths due to all causes.
Risks were identified in medical history via search criteria for MACE.
Patients with multiple events for a given preferred term were 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 7.3.8.12, CSR MVT-601-3201.

When the incidence of MACE was adjusted for exposure to treatment, the difference between the relugolix and leuprolide groups remained: the exposure-adjusted event rate for an adverse event associated with MACE was 3.3 in the relugolix group and 7.0 in the leuprolide group. The cumulative incidence of MACE in all patients for the primary analysis of study MVT-601-3201 is shown in

Figure 23.

Figure 23. Cumulative Incidence of Major Adverse Cardiovascular Events (Primary Analysis Safety Population)



The database lock date for the primary analysis was 10 Dec 2019.
Abbreviations: CI = confidence interval.
Source: Figure 18, MVT-601-3201 Primary Analysis CSR.

The Kaplan-Meier curves for time to MACE 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 were for the relugolix group 2.84% (95% CI: 1.77%, 4.53%) compared with the leuprolide group at 5.62% (95% CI: 3.53%, 8.89%).

Justification for unadjudicated MACE

The MACE events used in above post-hoc analysis were not adjudicated; however, the reported events and patient narratives provided are largely 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).

Events of MACE were collected according to standard practice for adverse event collection, underwent 100% source data verification with study monitors at the study site to assess for any missing adverse event data, particularly serious adverse events. Furthermore, medical review of each individual patient profile was conducted prior to database lock to reconcile any new concomitant medication use with reported adverse events to ensure adverse events requiring medication were not missed.

This analysis was performed as part of the assessment of safety and, therefore, was not a key endpoint in the study; 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 occurring by chance in this large randomized prospective trial in a population of patients with comparable cardiovascular history and risk factors at baseline.

Finally, the study used the SMQ for MACE as agreed with the FDA *prior to database lock*.

Ischemic heart disease

A medical history of ischemic heart disease, identified by applying the Ischemic Heart Disease SMQ to medical history data, was reported similarly between the treatment groups (12.2% of patients in the relugolix group vs. 14.6% of patients in the leuprolide group). In a post hoc analysis, generally similar proportions of patients without a medical history of ischemic heart disease in both groups reported adverse events associated with ischemic heart disease (1.8% and 1.1%, respectively), see

Table 51.

Table 51. Summary of Ischemic Heart Disease with or without a Medical History of Ischemic Heart Disease by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

	Relugolix 120 mg QD (N = 622)		Leuprolide (N = 308)	
Preferred Term	**Patients with IHD MH (N = 76)**	**Patients without IHD MH (N = 546)**	**Patients with IHD MH (N = 45)**	**Patients without IHD MH (N = 263)**
Patients with at least one AE of ischemic heart disease, n (%)	5 (6.6%)	10 (1.8%)	2 (4.4%)	3 (1.1%)
Odds ratio (95% CI) within treatment group (with IHD MH vs without IHD MH)	3.8 (1.3, 11.4)		4.0 (0.7, 24.8)	
Odds ratio (95% CI) between treatment group (leuprolide vs relugolix)			0.7 (0.1, 3.6)	0.6 (0.2, 2.3)
Acute myocardial infarction	1 (1.3%)	4 (0.7%)	1 (2.2%)	0
Coronary artery disease	1 (1.3%)	1 (0.2%)	0	0
ECG signs of myocardial ischaemia	0	2 (0.4%)	0	0
Myocardial infarction	2 (2.6%)	0	0	0
Acute coronary syndrome	0	1 (0.2%)	0	0
Angina pectoris	0	1 (0.2%)	0	2 (0.8%)
Coronary artery occlusion	0	1 (0.2%)	0	0
Coronary artery stenosis	0	1 (0.2%)	0	0
Electrocardiogram ST segment elevation	0	1 (0.2%)	0	0
Electrocardiogram ST-T segment depression	0	1 (0.2%)	0	0
Myocardial ischaemia	1 (1.3%)	0	1 (2.2%)	0
Troponin increased	0	1 (0.2%)	0	0
Angina unstable	0	0	0	1 (0.4%)

Abbreviations: AE = adverse event; CSR = clinical study report; ECG = electrocardiogram; IHD = ischemic heart disease; MH = medical history; N = number of patients in the treatment group; n=number of patients with specified AE; QD = once daily; SMQ = standardised MedDRA Query.
Search criteria included Ischaemic Heart Disease SMQ (broad).
Risks were identified in medical history via search criteria for IHD.
Patients with multiple events for a given preferred term were 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 7.3.8.18, MVT-601-3201 Primary Analysis CSR.

After 48 weeks of treatment, the Kaplan-Meier estimates of ischemic heart disease rate in all patients was 2.20% (95% CI: 1.28%, 3.76%) in the relugolix group and 1.67% (95% CI: 0.70%, 3.96%) in the leuprolide group (hazard ratio = 1.4813; 95% CI: 0.5384, 4.0755).

Loss of Bone Mineral Density

Bone mineral density loss is associated with testosterone deficiency in men, based on the mechanism of action for both GnRH agonists and antagonists, where hormone levels are decrease to castrate-levels for a longer period of time.

In the relugolix development program, early studies included the use of dual-energy x-ray absorptiometry (DXA) scans to assess bone density. Monitoring in subsequent studies included reporting of all fractures as adverse events. The use of concomitant bone-modifying agents such as denosumab or a bisphosphonate could also be recommended for some patients to decrease risk of pathologic fractures and other skeletal events during clinical studies which was at the discretion of the treating investigator.

Bone mineral density with bone densitometry was not assessed in the pivotal study MVT-601-3201 as the 48-week treatment duration was not expected to result in clinically relevant bone mineral density loss in this patient population treated for advanced prostate cancer. In the primary analysis of study MVT-601-3201, bone health events were reported for similar proportions of patients in both the relugolix group (20 patients [3.2%]) and the leuprolide group (12 patients [3.9%]). The proportion of patients with fracture-related AEs was also similar between the two groups (1.4 and 1.0%, respectively).

The AEs reported in the Primary Analysis Safety Population are summarized by preferred term in Table 52.

Table 52. Summary of Loss of Bone Mineral Density by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

Preferred Term	Relugolix 120 mg QD (N = 622)	Leuprolide (N = 308)
Patients with at least one AE of loss of bone mineral density, n (%)	20 (3.2%)	12 (3.9%)
Osteopenia	3 (0.5%)	2 (0.6%)
Pathological fracture	3 (0.5%)	2 (0.6%)
Fibula fracture	2 (0.3%)	0
Foot fracture	2 (0.3%)	0
Osteoporosis	2 (0.3%)	1 (0.3%)
Rib fracture	2 (0.3%)	0
Femoral neck fracture	1 (0.2%)	0
Femur fracture	1 (0.2%)	0
Hand fracture	1 (0.2%)	3 (1.0%)
Hip fracture	1 (0.2%)	0
Spinal compression fracture	1 (0.2%)	0
Traumatic fracture	1 (0.2%)	0
Ankle fracture	0	2 (0.6%)
Bone density decreased	0	2 (0.6%)
Wrist fracture	0	1 (0.3%)

Preferred Term	Relugolix 120 mg QD (N = 622)	Leuprolide (N = 308)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; QD = once daily; SMQ = standardised MedDRA Query.
Search criteria included Osteoporosis/Osteopenia SMQ (broad) and all preferred terms including the term Fracture, excluding Tooth fracture and Fracture of penis.
Patients with multiple events for a given preferred term were 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 7.3.8.2, CSR MVT-601-3201.

DXA

In Study *C27002*, bone loss was monitored. Bone health-related events were reported in 8 patients (7.3%; osteopenia [3 patients], hand fracture [2 patients], osteoporosis, BMD decrease, cervical vertebral fracture [1 patient each]) in the relugolix group. The events in five of the 8 patients were assessed by the investigator as drug-related. In the leuprorelin group there were no bone health-related adverse events reported. During the study, BMD was monitored by DXA at baseline and Week 49 in both groups and, although there was some variation within each group there were no clinically important differences observed in percent change over time on T-score. For all treatment groups, N-telopeptide was increased from baseline at both Week 13, Day 1 and Week 49, Day 1. Median percent changes from baseline at Week 49, Day 1 were approximately 32% and 43% in the relugolix 80-mg and 120-mg groups, respectively, and approximately 16% in the leuprorelin group. Median change measured by DXA was -2%, -1.6% in the relugolix 80-mg and 120-mg groups, respectively, and -2.5% in the leuprorelin group.

QTc prolongation

In the pivotal study, AEs related to QTc prolongation were searched for using the Torsade de pointes/QT prolongation SMQ (broad). AEs potentially related to QTc prolongation were reported for a similar proportion of patients in both pooled relugolix and leuprolide groups (2.1% vs. 1.9%, respectively. The adverse events are summarized by preferred term for the Primary Analysis Safety Population in

Table 53.

Table 53. Summary of QTc Prolongation by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

Preferred Term	Relugolix 120 mg QD (N = 622)	Leuprolide (N = 308)
Patients with at least one AE of QTc prolongation, n (%)	13 (2.1%)	6 (1.9%)
Syncope	8 (1.3%)	3 (1.0%)
Electrocardiogram QT prolonged	4 (0.6%)	0
Loss of consciousness	1 (0.2%)	0
Cardio-respiratory arrest	0	3 (1.0%)
Multiple organ dysfunction syndrome	0	1 (0.3%)

Abbreviations: AE = adverse event; CSR = clinical study report; N = number of patients in the treatment group; n = number of patients with specified AE; QTc = corrected QT interval; QD = once daily; SMQ = standardised MedDRA Query.
Search criteria included Torsade de pointes/QT prolongation SMQ (broad).
Patients with multiple events for a given preferred term were 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: Table7.3.8.3, CSR MVT-601-3201.

Electrocardiograms (12-lead) were obtained at the screening 3 visit, the baseline (Day 1), Week 5, Week 13, Week 25, Week 49/early termination visit, and the safety follow-up visit. A total of 36 patients (27 patients [4.3%] in the relugolix group and 9 patients [2.9%] in the leuprolide group) had an ECG that was interpreted as abnormal and clinically significant. The study did not collect details of ECGs besides the investigator's determination of clinical significance. In study C27002, ECGs were obtained throughout the study and interval data entered in 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 ≤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.

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.

Second primary malignancies

In the pivotal study MVT-601-3201, a post hoc analysis was performed to evaluate the occurrence and type of second primary malignancies. This analysis is summarized by treatment group and cumulatively over time (0-12, 0-24, 0-36, and 0-48 weeks) in Table 54.

Table 54. Second Primary Malignancy Events by Decreasing Frequency of Preferred Term by Time Period, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

	Time Period				
Treatment Group Preferred Term	**0 - 12 Weeks**	**0 - 24 Weeks**	**0 - 36 Weeks**	**0 - 48 Weeks**	**Any**
Relugolix 120 mg QD (N = 622)					

Patients with at least one AE of malignant tumours, n (%)	6 (1.0%)	9 (1.4%)	13 (2.1%)	19 (3.1%)	19 (3.1%)
Basal cell carcinoma	3 (0.5%)	3 (0.5%)	4 (0.6%)	7 (1.1%)	7 (1.1%)
Squamous cell carcinoma of skin	0	2 (0.3%)	3 (0.5%)	3 (0.5%)	3 (0.5%)
Adenocarcinoma of colon	1 (0.2%)	1 (0.2%)	2 (0.3%)	2 (0.3%)	2 (0.3%)
Bladder transitional cell carcinoma stage II	0	0	1 (0.2%)	1 (0.2%)	1 (0.2%)
Bowen's disease	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Lip squamous cell carcinoma	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Malignant melanoma in situ	0	0	0	1 (0.2%)	1 (0.2%)
Malignant melanoma stage I	0	0	0	1 (0.2%)	1 (0.2%)
Non-small cell lung cancer metastatic	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Small cell lung cancer metastatic	0	0	0	1 (0.2%)	1 (0.2%)
Transitional cell cancer of the renal pelvis and ureter	0	0	0	1 (0.2%)	1 (0.2%)
Leuprolide (N = 308)					
Patients with at least one AE of malignant tumours, n (%)	0	0	1 (0.3%)	3 (1.0%)	3 (1.0%)
Basal cell carcinoma	0	0	0	1 (0.3%)	1 (0.3%)
Squamous cell carcinoma of skin	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)
Transitional cell carcinoma	0	0	0	1 (0.3%)	1 (0.3%)

Abbreviations:AE = adverse event; CSR = clinical study report;
N = number of patients in the treatment group; n = number of patients with specified AE; QD = once daily;
SMQ = Standardised MedDRA Query.
Malignant tumors includes Malignant tumours SMQ (narrow) excluding terms containing 'prostate' or 'metastases'.
Patients with multiple events for a given preferred term are counted only once for each preferred term.
Events are sorted by system organ class alphabetically and then by decreasing frequency of preferred term.
Time to initial onset of adverse events is used.
MedDRA Version 22.0.
Source:Table 7.3.8.30, MVT-601-3201 Primary Analysis CSR.

Second primary malignancies were reported more often in the relugolix group (19 patients [3.1%]) compared with the leuprolide group (three patients [1.0%]). There was no clear imbalance for a specific tumour type. In the relugolix group there was an even distribution over the 48-week period.

In study C27002, two relugolix patients (1.8%) reported a second primary malignancy, including one patient with bladder cancer reported on Day 28 and one patient with basal cell carcinoma reported on Day 136 [both in the relugolix 80-mg group]). There were no reports of second primary malignancies in the leuprorelin group.

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 oesophageal cancer was reported at week 85 in the open-label expansion phase of the study (ie, study Day 597).

2.6.8.4. Laboratory findings

Biochemistry

In the MVT-601-3201 Primary Analysis Safety Population, 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.

Median creatinine levels at baseline were similar in the relugolix and leuprolide groups (83.0 µmol/L and 84.0 µmol/L, respectively) and remained similar at Week 49 Day 1 (Day 337) (81.0 µmol/L and 80.0 µmol/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 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).

Results for ALT and AST and parameters related to glucose/lipid metabolism are summarized with adverse events of clinical interest.

Haematology

In the MVT-601-3201 Primary Analysis Safety Population, mean haematology laboratory values at baseline and subsequent time points were generally consistent across the treatment groups for all parameters. Furthermore, for haematology 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.

Median **haemoglobin** levels at baseline were within the normal range for both groups: 144.0 g/L in the relugolix group and 143.0 g/L in leuprolide group. The median haemoglobin 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 haemoglobin during the study (68.8% and 67.5%, respectively).

The proportion of patients with haemoglobin ≤ 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 anaemia at baseline and developed grade ≥ 3 anaemia during the study. One patient (0.2%) in the relugolix group with normal platelet values at baseline had grade 4 decreased platelets postbaseline, compared with no patients in the leuprolide group. Two separate nonserious adverse events of grade 3 platelet count decreased were reported for both occurrences.

Median **platelet** values at baseline were similar in the relugolix group (218.5.0 × 109/L) and the leuprolide group (214.0 × 109/L) and slightly increased at Week 49 Day 1 (Day 337) in both groups (226.0 × 109/L and 222.0 × 109/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 × 109/L during the study were comparable in both groups (0.5% in relugolix group and 0.6% in leuprolide group).

Other prostate cancer studies

In study **C27003**, mean haemoglobin levels declined over time for both the relugolix group and degarelix group. At baseline, mean haemoglobin 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 haemoglobin 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 discontinuation of study drug treatment. The maximum post baseline shift in platelet count was grade 1 (relugolix 14%, degarelix 21%). In the individual supportive studies, there were no clear imbalances or trends in changes of haematology parameters following treatment with relugolix.

Vital signs

A summary of patients with potentially clinically significant postbaseline abnormalities in vital signs at two or more visits is presented in Table 55.

Table 55. Potentially Clinically Significant Abnormalities in Vital Signs Results in Two or More Consecutive Visits, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

Patients with Potentially Clinically Significant Abnormalities in ≥2 Postbaseline Consecutive Visi n (%)	Relugolix 120 mg QD (N = 622)	Leuprolide (N = 308)	Total (N = 930)
Systolic blood pressure[a]			
≥ 140 mmHg	341 (54.8%)	174 (56.5%)	515 (55.4%)
≥ 180 mmHg	4 (0.6%)	2 (0.6%)	6 (0.6%)
≤ 90 mmHg	2 (0.3%)	2 (0.6%)	4 (0.4%)
≥ 140 mmHg and > highest screening or baseline	193 (31.0%)	101 (32.8%)	294 (31.6%)
≥ 180 mmHg and > highest screening or baseline	4 (0.6%)	2 (0.6%)	6 (0.6%)
≤ 90 mmHg and < lowest screening or baseline	2 (0.3%)	2 (0.6%)	4 (0.4%)
≥ 20 mmHg increase from baseline	94 (15.1%)	49 (15.9%)	143 (15.4%)
≥ 20 mmHg decrease from baseline	133 (21.4%)	59 (19.2%)	192 (20.6%)
Diastolic blood pressure[a]			
≥ 90 mmHg	138 (22.2%)	69 (22.4%)	207 (22.3%)
≥ 105 mmHg	2 (0.3%)	2 (0.6%)	4 (0.4%)
≤ 50 mmHg	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 90 mmHg and > highest screening or baseline	95 (15.3%)	45 (14.6%)	140 (15.1%)
≥ 105 mmHg and > highest screening or baseline	2 (0.3%)	2 (0.6%)	4 (0.4%)
≤ 50 mmHg and < lowest screening or baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 15 mmHg increase from baseline	52 (8.4%)	33 (10.7%)	85 (9.1%)
≥ 15 mmHg decrease from baseline	74 (11.9%)	39 (12.7%)	113 (12.2%)
Heart rate[a]			
≥ 120 bpm	2 (0.3%)	0 (0.0%)	2 (0.2%)
< 45 bpm	4 (0.6%)	2 (0.6%)	6 (0.6%)
≥ 120 bpm > highest screening or baseline	2 (0.3%)	0 (0.0%)	2 (0.2%)
< 45 bpm and < lowest screening or baseline	2 (0.3%)	2 (0.6%)	4 (0.4%)
≥ 15 bpm increase from baseline	105 (16.9%)	49 (15.9%)	154 (16.6%)
≥ 15 bpm decrease from baseline	67 (10.8%)	32 (10.4%)	99 (10.6%)

Abbreviations: CSR = clinical study report; N = number of patients in the treatment group; n = number of patients included in the summary statistics; QD = once daily.
Baseline value is defined as the last measurement on or before the first administration date of study drug. If time is available, the baseline value is defined as the last measurement before the first administration date and time of study drug.
[a]Postbaseline treatment-emergent values for two or more consecutive visits. Patients can be summarized in more than one row.
Source: Table 7.3.10.3, MVT-601-3201 Primary Analysis CSR.

Electrocardiograms

A total of 36 patients (27 patients [4.3%] in the relugolix group and nine patients [2.9%] in the leuprolide group) had an ECG that was interpreted as abnormal and clinically significant.

2.6.8.5. In vitro biomarker test for patient selection for safety

n/a

2.6.8.6. Safety in special populations

Subgroup analyses were performed for the pivotal study MVT-601-3201 Final Analysis Safety Population using the intrinsic factors (age, race, ethnicity, and diagnosis [presence or absence of metastatic disease]).

Age

1. **Table 56. Overall Summary *of Adverse Events by Age Group***

MedDRA System Organ Class or Preferred Terms	Age < 65 (n = 139) n (%)	Age 65-74 (n = 327) n (%)	Age 75-84 (n = 224) n (%)	Age ≥ 85 (n = 27) n (%)
Total Adverse Events (AEs)	952	1959	1256	176
No. of patients with at least one AE, n (%)	127 (91.4%)	304 (93.0%)	209 (93.3%)	24 (88.9%)
Serious AEs No. of patients with at least one serious AE, n (%)	12 (8.6%)	39 (11.9%)	33 (14.7%)	5 (18.5%)
Fatal	0	8 (2.4%)	1 (0.4%)	1 (3.7%)
Hospitalization/prolong existing hospitalization	12 (8.6%)	34 (10.4%)	31 (13.8%)	5 (18.5%)
Life-threatening	0	3 (0.9%)	2 (0.9%)	1 (3.7%)
Disability/incapacity	1 (0.7%)	1 (0.3%)	0	1 (3.7%)
Other (medically significant)	0	6 (1.8%)	8 (3.6%)	1 (3.7%)
AE leading to drop-out[a]	5 (3.6%)	11 (3.4%)	6 (2.7%)	4 (14.8%)
Psychiatric disorders SOC[b]	27 (19.4%)	52 (15.9%)	27 (12.1%)	4 (14.8%)
Nervous system disorders SOC[b]	37 (26.6%)	63 (19.3%)	49 (21.9%)	9 (33.3%)
Accidents and injuries[c]	18 (12.9%)	36 (11.0%)	29 (12.9%)	5 (18.5%)
Cardiac disorders SOC[b]	9 (6.5%)	33 (10.1%)	21 (9.4%)	2 (7.4%)
Vascular disorders SOC[b]	94 (67.6%)	197 (60.2%)	117 (52.2%)	14 (51.9%)
Cerebrovascular disorders[d]	0	1 (0.3%)	1 (0.4%)	1 (3.7%)
Infections and infestations SOC[b]	43 (30.9%)	116 (35.5%)	77 (34.4%)	9 (33.3%)
Anticholinergic syndrome[e]	0	0	0	0
Quality of life decreased[f]	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[g]	15 (10.8%)	27 (8.3%)	31 (13.8%)	4 (14.8%)
Other AE appearing more frequently in older patients				
Cataract	1 (0.7%)	6 (1.8%)	10 (4.5%)	0
Fall	2 (1.4%)	9 (2.8%)	13 (5.8%)	3 (11.1%)
Decreased appetite	3 (2.2%)	9 (2.8%)	11 (4.9%)	5 (18.5%)

a Represents adverse events leading to study drug discontinuation.
b Based on search of MedDRA SOC term.
c Accidents and injuries: based on search of MedDRA SOC terms - Injury, poisoning, and procedural complications.
d Cerebrovascular disorders: based on search of HLGT Central nervous system vascular disorders.
e Anticholinergic syndrome: based on search of preferred term "Anticholinergic syndrome".
f Quality of life decreased: based on search of preferred term "Quality of life decreased".

g Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures: Based on search of preferred terms - Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, and any preferred term containing word with fracture. Source: Table 8.3.1.1.1 Database lock date 23Sep2020

For the relugolix group of the final analysis safety population, 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 SAEs and of AEs leading to study drug discontinuation. Additionally, the incidence of adverse cardiovascular events was highest for the oldest (≥ 85 years) subgroup (7.4%) compared with other age subgroups (ranging from 2.9% to 4.9%).

The incidence of carbohydrate and lipid metabolic effects and mood disorders was highest in the youngest (< 65 years) subgroup (12.2% and 9.4%, respectively) compared with the other age subgroups (ranging from 3.7% to 7.6% and from 0% to 4.9%, respectively).

Race

The overall distributions of adverse events for the race subgroups of Asian, Black/African American, and White in the final analysis safety population were generally similar, except that the Black/African American subgroup had the highest incidence of adverse events considered to be related to study drug (91.2% for relugolix) compared with the White subgroup (75.2%) or the Asian subgroup (64.3%). 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 (5.9% for relugolix) than for the White subgroup (14.0%) or the Asian subgroup (10.2%).

Ethnicity

The overall distributions of adverse events for the ethnicity subgroups of Not Hispanic or Latino (N =640), and Hispanic or Latino (N =64) in the final analysis safety population were generally similar (91.7% vs. 100%, respectively). The Not Hispanic or Latino subgroup had a lower incidence of adverse events leading to study drug discontinuation (3.1% for relugolix) compared with the Hispanic or Latino subgroup (9.4% for relugolix).

2.6.8.7. Safety related to drug-drug interactions and other interactions

Relugolix is a P-gp substrate and co-administration with oral P-gp inhibitors increase the area under the curve (AUC) and the maximum concentration (Cmax) of relugolix, which may increase the risk of adverse reactions associated with Orgovyx. Co-administration with erythromycin, a P-gp and moderate CYP3A inhibitor, increased the AUC and Cmax of relugolix by 3.5- and 2.9-fold respectively, due to inhibition of intestinal P-gp by erythromycin, which resulted in an increase in the oral bioavailability of relugolix.

2.6.8.8. Discontinuation due to adverse events

A summary of AEs that led to study drug withdrawal by preferred term is presented for the Primary Analysis Safety Population in Table 57.

Table 57. Adverse Events Leading to Study Drug Withdrawal by Preferred Term, Pivotal Phase 3 Study MVT-601-3201, Primary Analysis Safety Population

Preferred Term	Relugolix 120 mg QD (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
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; N = number of patients in the treatment group; n = number of patients with specified AE; QD = once daily.
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.
MedDRA Version 22.0.
Source: Table 7.3.4.2, CSR MVT-601-3201.

In study MVT-601-3201, AEs 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. The incidence of AEs that led to withdrawal or fatal outcome was comparable between the relugolix group (3.9%) and the leuprolide group (3.2%).

This imbalance for withdrawal is likely due to the fact that the study drug is given as a daily oral dose and the control leuprolide as a 3-month depot formulation.

There were no AEs resulting in study drug withdrawal reported for more than one patient, except atrioventricular block second degree (in two patients in the relugolix group and no patient in the leuprolide group).

No pattern of events leading to study drug withdrawal was noted in the supportive prostate cancer studies.

2.6.8.9. Post marketing experience

Relugolix monotherapy is approved for separate indications in two countries, Japan (40 mg, uterine fibroid indication) and the US (120 mg, advanced prostate cancer indication), respectively.

No post marketing data are available for relugolix 120 mg in advanced prostate cancer patients as the product was only launched on 04 January 2021 in the US.

From 01 March 2019 to 07 July 2020, 23 SAEs were reported on 6,293,000 patient-days in relatively healthy female patients of fertile age. SAEs that may be applicable to the current male patient group of advanced prostate cancer patients are 2 cases of anaphylactic reaction, 1 case of drug eruption and malaise, 1 case of hypertension, 1 case of pulmonary embolism, and 1 case of multiple sclerosis relapse.

2.6.9. Discussion on clinical safety

Like degarelix, relugolix is a GnRH-receptor antagonist, so there is previous safety experience. Further, a large amount of safety experience is available from GnRH agonists, which, although after an initial flare up of testosterone of about one month, have a comparable degree of testosterone suppression. In the current dossier, the primary safety data are derived from the comparative pivotal phase 3 study versus leuprorelin 3-month depot-injection MVT-601-3201, which is divided as follows:

- Pivotal phase 3 study (MVT-601-3201)
  - Primary Analysis Safety Population
  - Final Analysis Safety Population
  - Metastatic Patient Safety Population

Supportive safety data include:

- Other Prostate cancer studies (C27002 phase 2 study versus leuprorelin in patients with advanced prostate cancer, phase 2 study C27003 versus degarelix (GnRH-antagonist) in participants with localized prostate cancer + radiotherapy and phase 1 study TB-AK160108 in hormone treatment-naïve participants with non-metastatic prostate cancer.

- In addition, the discussion of liver safety also includes adverse events of clinical interest from the clinical pharmacology studies and for the pooled Women's Health 12-Week Monotherapy Safety Population. In the sections for discussion of hypersensitivity and QT prolongation, relevant data from the clinical pharmacology studies also are presented.

Patient exposure. The primary safety analysis included 622 patients in the relugolix group and 308 patients in the leuprorelin group. The safety analysis included 717 and 357 patients in the relugolix and leuprolide group, respectively.

The primary analysis of safety and efficacy occurred after 934 patients were randomized to the study (Cohort 1) and completed the 48-week treatment period and 30-day safety follow-up visit or

discontinued early. The final analysis of the study occurred after 434 patients with metastatic disease (of whom 295 patients were also included in the primary analysis [Cohort 1]) were randomized to the study (Cohort 1 and Cohort 2) and completed the 48-week treatment period and 30-day safety follow-up visit or discontinued early. The study remains ongoing.

In this phase 3 study, a total of 298 patients received relugolix 102 mg after an initial bolus of 360 mg and 238 received the GnRH-agonist leuprorelin for more than 48 weeks. The mean duration of relugolix use was 45.52 weeks. Overall, the documented safety exposure to relugolix exceeds the requirements of ICH-E1 and is considered sufficient for adequate assessment of the safety profile of relugolix in patients with advanced prostate cancer.

Adverse events profile. In the primary analysis of the pivotal study, AEs were frequently reported with similar incidence for the two treatment groups: 578 patients (92.9%) in the relugolix group and 288 patients (93.5%) in the leuprolide group. Of note, in the pivotal study MVT-601-3201, as is standard procedure, patients in the leuprolide group could receive an antiandrogen for the first 4 weeks or longer if indicated for disease flare management (temporary increase in testosterone which could lead to disease exacerbation) in the opinion of the investigator. Additionally, bone preserving medication was permitted at the discretion of the Investigator.

Common adverse events. The mechanism of action of GnRH agonists and antagonists is well understood. In general, the reported adverse events are in line with those known for androgen deprivation therapy. In the primary analysis of study MVT-601-3201, the most commonly reported (>10% patients) adverse events in any treatment group included hot flush, fatigue, constipation, diarrhoea, arthralgia, and hypertension. Constipation, diarrhoea, and arthralgia were reported at a greater incidence on relugolix, cardiovascular adverse events were seen more on leuprolide. Constipation, diarrhoea, and musculoskeletal pain (which includes arthralgia) are included in Section 4.8 of the proposed SmPC for relugolix as 'very common' adverse drug reactions. The supportive prostate cancer studies showed a similar pattern of common AEs.

Serious adverse events. The incidence of serious adverse events was lower for the relugolix group (12.2%; 76 patients) compared with leuprolide (15.3%; 47 patients). Drug-related serious adverse events were reported in both groups (six patients [1.0%] in the relugolix group and three patients [1.0%] in the leuprolide group). Serious adverse event that was a grade 3 maximum severity occurred in 8.0% of the relugolix group and 10.1% of the leuprolide group). No pattern indicative for a safety signal could be identified among the types of drug-related SAEs, which is reassuring.

AEs of special interest. Safety parameters of clinical interest represent prespecified categories of adverse events that are either:

- known toxicities of androgen deprivation therapy (ADT) with GnRH receptor agonists (carbohydrate and lipid metabolic effects, adverse cardiovascular events, loss of bone mineral density, QTc prolongation, mood disorders, and vasomotor symptoms),
- potential risks associated with relugolix based on nonclinical data (hepatic transaminase elevations), or
- theoretical risks with an investigational agent (hypersensitivity).

Frequencies of general adverse events of special interest were comparable in both groups, although there were some small differences.

- ***Vasomotor symptoms***

Vasomotor symptoms (including mainly hot flush but also the terms hyperhidrosis, feeling hot, night sweats, and flushing) are known side effects of androgen deprivation therapy with GnRH receptor agonists. These were reported with the same incidence on relugolix (56.1%) and leuprolide (54.9%). Hot flush was the most common adverse event followed by hyperhidrosis and are listed in the proposed SmPC as adverse drug reactions.

- ***Hepatic transaminase elevations***

The evaluation of potential for hepatic transaminase elevations (ALT/AST) is based on non-clinical observations in monkeys exposed to a 48-times higher dose of relugolix, the clinical trial data, and data reported for drugs that work on the hypothalamic-pituitary-gonadal axis (GnRH receptor agonists [eg, leuprolide] and the GnRH receptor antagonists [eg, elagolix, degarelix). In the primary analysis of study MVT-601-3201, there were 13 patients with an adverse event of clinical interest (ALT and/or AST ≥ 3× ULN) reported during the study, 9 (1.4%) on relugolix and 4 (1.3%) on the leuprolide control. The proportion of patients with laboratory values meeting predefined limits of change at any time for ALT or AST were also similar in both treatment groups (7.6% vs 5.5%, respectively). One serious adverse event of grade 4 liver function test abnormal was reported for a patient with widely metastatic disease in the leuprolide group; no action was taken with study drug leuprolide (this is also not possible as this is a 3-month depot formulation). One patient on relugolix discontinued study drug due to alanine aminotransferase increased. Although there were more adverse events identified per the Drug-Related Hepatic Disorders SMQ in the relugolix group, specifically the terms alanine aminotransferase increased and aspartate aminotransferase increased, mean ALT and AST concentrations over time were similar in both treatment groups.

In the SmPC section 4.8 'ALT increased' is included as an uncommon ADR and the following description is given below the table: "*Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) concentrations > 3xULN were reported for 1.4% of patients with normal values prior to treatment, following treatment with relugolix. An increase to grade 3/4 ALT was observed in 0.3% of patients and to grade 3/4 AST in 0% of patients treated with relugolix, respectively. No events were associated with increased bilirubin*."

However, as similar reporting of the PT term ASAT increased compared to ALAT increased and convergent data from laboratory findings were noted, ASAT increased is added in section 4.8 of the SmPC.

- ***Carbohydrate and lipid metabolic effects: glucose metabolism***

Adverse events related to abnormal glucose metabolism were reported in both relugolix (5.8%) and leuprolide (6.2%) groups in the pivotal phase 3 study. 'Diabetes mellitus' was reported with a higher incidence on relugolix (3.7%) compared to leuprolide (1.9%); however, for ' type 2 diabetes mellitus' this was lower with relugolix compared to leuprolide (0.5% and 1.9%, respectively). Most events of diabetes mellitus were exacerbations of existing diabetes. Glucose increased is included in the proposed PI as a common ADR.

Adverse events related to abnormal lipid metabolism were similar in both groups (3.1% in the relugolix group and 2.3% in the leuprolide group). Individual events (including blood cholesterol increased, blood triglycerides increased, hypertriglyceridemia, dyslipidaemia, hypercholesterolaemia, and hyperlipidaemia) did not occur >1%, except Hypertriglyceridaemia in the leuprolide group (1.6%). Triglyceride increased is included in the proposed PI as a common ADR. Also reports of blood cholesterol increased and hypercholesterolemia AE as well as converging data from laboratory findings were noted, therefore blood cholesterol increased is also included in

section 4.8 of the SmPC. Of note, blood cholesterol increased is also listed in the product information of degarelix, another GnRH antagonist.

Of further interest, in section 4.4 and 4.8, other class warnings, such as glucose metabolism, has been included, in line with Degarelix**.**

- ***Hypersensitivity***

Hypersensitivity is a theoretical risk with a new investigational agent and is therefore investigated. In the primary analysis of study MVT-601-3201, incidence of adverse events related to hypersensitivity were reported for similar proportions of patients in both groups (44 patients [7.1%] in the relugolix group and 26 patients [8.4%] in the leuprolide group), with rash as the most common (3.2% and 2.3% of patients in each group, respectively). Therefore, the standard contraindication has been included ('Hypersensitivity to the active substance or to any of the excipients listed in section 6.1'). Additionally, 'rash' has been added in the ADR table in section 4.8.

- ***Mood disorders***

In the primary analysis of study MVT-601-3201, incidence of adverse events related to mood disorders were similar between relugolix and leuprolide (5.1% in the relugolix group and 4.5% in the leuprolide group), with depression as the most common (1.9% and 1.0% of patients in each group, respectively).

Long duration low testosterone with GnRH agonists or antagonists is associated with change in mood disorders. There is no unbalance or trend in the adverse events that appears to point to a different pattern with regard to mood disorders compared to leuprolide.

Depression is listed in the proposed prescribing information for relugolix (4.8), which is considered appropriate. It is also included in the SmPCs of degarelix (4.8) and leuprolide (4.4, 4.8).

- ***Loss of Bone Mineral Density (BMD)***

BMD loss is associated with testosterone deficiency in men, based on the mechanism of action for both GnRH agonists and antagonists, where hormone levels are decrease to castrate-levels for a longer period of time. BMD with bone densitometry was not assessed in the pivotal study MVT-601-3201 as the 48-week treatment duration was not expected to result in clinically relevant bone mineral density loss in this patient population treated for advanced prostate cancer.
Adverse events related to loss of bone mineral density were comparable between the two groups (3.2% and 3.9% of patients, respectively), as were the fracture-related adverse events (1.4% and 1.0% of patients, respectively).
For Study C27002, median percent changes in N-telopeptide from baseline at Week 49, Day 1 were approximately 32% and 43% in the relugolix 80-mg and 120-mg groups, respectively, and approximately 16% in the leuprorelin group. Median change in bone mineral density measured by DXA was -2%, -1.6% in the relugolix 80-mg and 120-mg groups, respectively, and -2.5% in the leuprorelin group.
A warning for changes in bone mineral density is included in the SmPC 4.4, and osteoporosis/osteopenia is included in the table in Section 4.8 of the SmPC.

- ***QTc Interval Prolongation***

QT-prolongation is a class effect of androgen deprivation therapy. Adverse events related to QTc prolongation were searched for using the Torsade de pointes/QT prolongation SMQ (broad).
In pivotal study MVT-601-3201, adverse events potentially related to QTc prolongation were reported for a similar proportion of patients in both pooled relugolix and leuprolide groups (2.1% vs. 1.9%, respectively. Clinically significant ECG abnormalities at ECG 12-lead screening were

found in 4.3% in the relugolix group and 2.9% in the leuprolide group. The study did not collect details of ECGs besides the investigator's determination of clinical significance.
The phase 1 dedicated thorough QT study with parallel design (60 mg, supratherapeutic 360 mg, placebo and positive control (moxifloxacin) did not suggest for any QT prolonging effect of relugolix with point estimates for the corrected ddQTcF around 5 ms and thus far below the 10 ms for regulatory concern.
For the relugolix SmPC a warning and precaution for the potential for QTc prolongation is reflected in SmPC section 4.4 to address the known effects of androgen deprivation on the QT interval and to include the results of the thorough QT study, in line with the SmPC of the GnRH-antagonist degarelix. Furthermore, QT-prolongation has been included in the SmPC in the table in Section 4.8. Of note, in the SmPC for Ryeqo (40 mg +E2/NETA) for women, no warning is given for QT prolongation.

- ***Adverse cardiovascular events***

Adverse cardiovascular events are a known side effect of androgen deprivation therapy. Studies have also found a higher risk of major cardiovascular events in patients with prostate cancer treated with GnRH receptor agonists compared with GnRH receptor antagonists, particularly in men with pre-existing cardiovascular disease.
In the pivotal study MVT-601-3201, after 48 weeks of treatment, adverse cardiovascular events were reported in less patients in the relugolix group: 24 (3.9%) of patients in the relugolix group and for 22 (7.1%) in the leuprolide group. Of note, the reporting rates retrieved may be increased in real life conditions considering exclusion of patients with previous significant cardiac conditions within 6 months in pivotal study.
Also MACE were reported in 18 patients [2.9%] patients in the relugolix group and 19 patients [6.2%] in the leuprorelin group. All but five of the MACE events were serious adverse events. Among the MACE, proportion of patients was smaller in the cardiovascular portion only: 9 (1.4%) patients on relugolix and 2 (0.6%) on leuprolide; deaths due to all causes: 7 (1.1%) and 9 (2.9%); MACE in patients with medical history of MACE: 3 (3.6%) and 8 (17.8%); and MACE in patients without medical history of MACE: 15 (2.8%) and 11 (4.2%). However, proportion of patients was larger for cerebrovascular portion only of MACE: 4 (0.6%) and 10 (3.2%); and ischemic heart disease: 15 (2.4%) and 5 (1.6%).
An assessment of risk factors (life-style risk factors, any cerebrovascular or cardiovascular risk factor, and any history of MACE) showed a similar proportion of patients in each group reporting any risk factor for cerebrovascular and/or cardiovascular disease (91.6% in the relugolix group and 94.2% in the leuprolide group); this was also the case across the three categories. When the incidence was adjusted for exposure to treatment, the exposure-adjusted event rate for an adverse event associated with MACE was 3.3 in the relugolix group and 7.0 in the leuprolide group. With regard to age, the incidence of adverse cardiovascular events for relugolix was highest for the oldest subgroup (≥ 85 years), 7.4% compared with other age subgroups (ranging from 2.9% and 4.9%).

Based on the results of the pivotal phase 3 study, it seems that there were less cardiovascular events and MACE observed on relugolix compared to leuprolide. However, MACE events were not adjudicated, but a MACE composite query by treatment group (Myocardial Infarction SMQ, Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ, and deaths due to all causes) and the Ischaemic Heart Disease SMQ (which contains two sub-SMQs, the Myocardial Infarction SMQ [broad] and the Other Ischaemic Heart Disease SMQ [broad]) was used in the prespecified safety analyses.

The Applicant gives as rationale for not using adjudicated cases, that the reported events were consistent with the 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); also, the SMQ for MACE was agreed with the FDA prior to database lock. Further, MACE was not a key endpoint in the study.

In this case, from a statistical viewpoint, there are relatively few MACE and adjudication would probably lower the number, thereby not increasing sensitivity (false negative turning positive) but only increasing specificity (removing false positives). Therefore, adjudication at this point may not be considered useful. However, the Applicant has also calculated a hazard ratio, including a statistically significant p-value. Such analysis is not acceptable when based on unadjudicated (and therefore not validated) data. Furthermore, the analysis method was not prespecified in the SAP, nor was the endpoint included in the hierarchical testing strategy. So, these results should not be included in the SmPC. However, cardiac disorders included the Adverse event table in section 4.8.

Further, section 4.4 of the SmPC includes a general warning on the risk of cardiovascular events, which is similar to the warning included in the SmPC of degarelix (Firmagon):

"Cardiovascular disease

Cardiovascular disease such as myocardial infarction and stroke has been reported in the medical literature in patients with androgen deprivation therapy. Therefore, all cardiovascular risk factors should be taken into account."

The inclusion of this general warning is considered acceptable.

- ***Second primary malignancies***

A post hoc analysis was performed to evaluate the occurrence and type of second primary malignancies. In the primary analysis of pivotal 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%]). There was no clear imbalance for a specific tumour type. In the relugolix group there was an even distribution over the 48-week period.

The most common in both groups were nonmelanoma skin cancers. According to the literature, the annual incidence in the general population appears to be at least 1%. The incidence of the other malignancies reported for the relugolix and leuprolide groups is generally consistent with the risks for these malignancies in older men. Overall, there is no apparent signal regarding the development of second primary malignancies during treatment with relugolix in patients with prostate cancer. Such events will continue to be monitored in routine pharmacovigilance.

Clinical laboratory findings

All clinical laboratory tests conducted throughout the study, including haematology, chemistry, urinalysis, and lipids, were comparable between the two groups.

Vital signs

No changes or trends were identified with regard to systolic and diastolic blood pressures and mean heart rates between the two groups or in time.

No changes or trends were identified with regard to ECG abnormalities. There were no obvious differences between the two groups in the pivotal study.

Safety in special populations

Subgroup analyses were performed for the study MVT-601-3201 Final Analysis Safety Population using the intrinsic factors (age, race, ethnicity, and diagnosis [presence or absence of metastatic disease]).

No specific patterns were identified that would suggest a differential safety profile of relugolix in the different subgroups of patients. Regarding age, the observations for the oldest subgroup did not appear to be driven by any particular type of AE; the sample size for the age subgroup of ≥ 85 years is small (N = 27 for relugolix and N = 19 for leuprolide), thus making comparisons with larger subgroups difficult to interpret. AEs reported more frequently in the older age groups include cataract, fall, and decreased appetite, all events associated with advancing age, independent of concomitant medication. There was no evidence of clustering of specific adverse events by age subgroup. Regarding race, interpretation of these findings is limited by the small sample size of the Black/African American subgroup (N =34 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. Regarding ethnicity, the observed differences between the two ethnicity subgroups did not appear to be attributable to any specific adverse event. Regarding parameters of clinical interest, the incidence of carbohydrate and lipid metabolic effects was lower for the Not Hispanic or Latino subgroup (8.1% for relugolix) than for those of Hispanic or Latino ethnicity (14.1%). No other notable differences were observed for the incidences of parameters of clinical 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).

Renal impairment

No important differences in safety findings were observed for relugolix in subgroups defined by renal function in the pivotal phase 3 study (MVT-601-3201) Final Analysis Safety Population. The overall distributions of adverse events for the three renal function subgroups (CrCl ≥ 30 to < 60, ≥ 60 to < 90, and ≥ 90 mL/min) were similar. However, for the severe renal function subgroup (CrCl <30 mL/min) only four subjects were included.

However, since the effect of severe renal impairment on the pharmacokinetics of relugolix does not fall within the comparability bounds of 0.50 to 1.50, the Applicant needs to mention this effect in the "Special warning and precautions for use" Section 4.4 of the SmPC. See previous section on clinical pharmacology.

Hepatic impairment

The mean half-life of relugolix in patients with mild or moderate hepatic impairment and healthy control subjects were comparable. See previous section**.**

No dose adjustments for Orgovyx in patients with mild or moderate hepatic impairment are required. The effects of severe hepatic impairment on the pharmacokinetics of relugolix have not been evaluated.

Deaths

Sixteen deaths were reported in study MVT-601-3201 at the time of the primary analysis (7 ([1.1%] in the relugolix group and 9 [2.9%] in the leuprolide group) and five deaths (4 relugolix, 1 leuprolide) were reported in study C27002. In the final analysis of study MVT-601-3201, five additional patients (three relugolix, two leuprolide) died (relugolix group acute respiratory failure, death [suspect metastatic prostate cancer], and myocardial infarction; leuprolide group: COVID-19 pneumonia and prostate cancer). All cases were assessed by the investigator as not related to study drug, with the exception of one fatal case that was considered possibly related: a 74-year old patient on relugolix for 138 days had a fatal acute myocardial infarction. There was no trends or pattern identified among the fatal cases.

Safety related to drug-drug interactions and other interactions

This is discussed under clinical pharmacology. In the SmPC section 4.5, a warning is given to avoid co-administration with Orgovyx and oral P-gp inhibitors, including how to handle if co-administration cannot be avoided.

Discontinuations due to AEs

In study 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. This imbalance for withdrawal is due to the fact that relugolix is given as a daily oral dose and the control leuprolide as a 3-month depot formulation which cannot be removed. There were no adverse events resulting in study drug withdrawal reported for more than one patient, except atrioventricular block second degree (in two patients in the relugolix group). No pattern of events leading to study drug withdrawal was noted in the supportive prostate cancer studies.

The safety data of the other prostate cancer studies (C27002, C27003, and TB-AK160108) are consistent with the safety findings observed in the pivotal phase 3 study MVT-601-3201.

2.6.10. Conclusions on the clinical safety

Generally, the safety profile of relugolix is in line with leuprorelin and reflects its mechanism of action as an ADT. The rate of MACE on relugolix compared with that of leuprolide seems to be lower, though because of statistical considerations, a low overall number of events and because the MACE events were not adjudicated, no definitive conclusion can be drawn. Additionally, the oral route of relugolix has an advantage over GnRH agonists, as the oral treatment can be discontinued immediately. Further advantage is the absence of an initial temporary increase in testosterone (flare-up) which may lead to disease exacerbation noted with GnRH-agonists, as with an GnRH-antagonist like relugolix testosterone levels decrease within days.

2.7. Risk Management Plan

2.7.1. Safety concerns

None.

2.7.2. Pharmacovigilance plan

Not applicable.

2.7.3. Risk minimisation measures

None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 08 January 2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Orgovyx (relugolix) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Orgovyx is indicated for the treatment of adult patients with advanced hormone-sensitive prostate cancer.

3.1.2. Available therapies and unmet medical need

During more than 60 years the treatment of choice in metastatic prostate cancer has been androgen depletion therapy (ADT). Currently androgen depletion is often introduced in the adjuvant setting or at PSA relapse without detectable metastases (EMA/CHMP/703715/2012 Rev. 2). Long-acting GnRH *agonists* are currently the main forms of ADT, delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly, basis (2021 EAU Guidelines on prostate cancer). Firmagon (degarelix) is a GnRH *antagonist*, just like relugolix, but it is delivered as a depot injection, just like the GnRH agonists. Its practical shortcoming, however, is the lack of a long-acting depot formulation with, so far, only a monthly formulation being available (2021 EAU Guidelines on prostate cancer). It was approved in 2009 for the treatment of adult male patients with advanced hormone-dependent prostate cancer (Firmagon SmPC). This approval was mainly based on the pivotal, randomized, open-label phase 3 study CS21 of degarelix vs leuprolide in patients with prostate cancer requiring ADT (Klotz et al. BJU Int. 2008; Firmagon MAA EPAR).

It has been stated in scientific literature that the potential benefits of a daily-dosed oral agent could be multiple: ADT without an injectable depot (1) offers a more patient-friendly alternative with limited health care provider visits or procedures and no risk of local site reactions; (2) allows more flexible dosing and an option for prompt cessation of treatment due to intolerance or treatment-related side effects; and (3) eliminates the need for a lead-in antiandrogen to counteract potential testosterone flare induced with LHRH agonist-based treatments (Sachdev et al. Eur Urol. 2020). However, oral ADT is not without its own drawbacks. Depot formulation can offer reliable, sustained plasma delivery without reliance on patient adherence, interactions with other oral medications, or gastrointestinal absorption. The bothersome side-effect profile of ADT may lead to earlier cessation or interruption of oral therapy by patients. Furthermore, while in studies good adherence to oral dosing of medications may be shown, real-life compliance to long-term daily dosing is likely to be less optimal. Lastly, it is unclear if more rapid testosterone recovery would make the drug effect of the same nominal duration as in trials using GnRH agonist depot injection-based treatment (Sachdev et al. Eur Urol. 2020), and a shorter duration of testosterone suppression with relugolix (due to faster testosterone recovery) could lead to undertreatment given that cancer control has been associated with the duration of testosterone suppression (Mahal et al. Eur Urol. 2020). In conclusion, whereas there is perhaps not a high unmet medical need for an oral formulation of a GnRH receptor antagonist, it can be considered a valuable addition to the treatment armamentarium for advanced hormone-dependent prostate cancer.

3.1.3. Main clinical studies

In the pivotal, randomized, open-label phase 3 study **MVT--601-3201** (Shore et al. N Engl J Med. 2020) the safety and efficacy of oral relugolix vs leuprolide depot injections was evaluated in adult

patients with androgen-sensitive advanced prostate cancer who required at least 1 year of continuous ADT for the management of their disease and who were not candidates for surgical or radiation therapy with curative intent. A total of 624 patients were randomized (2:1) to receive relugolix- (360 mg on Day 1 followed by 120 mg QD for 48 weeks) and 310 patients were randomized to receive leuprolide (22.5 mg Q12W for 48 weeks).

3.2. Favourable effects

- In the relugolix group, 96.7% of patients (95% CI: 94.9%, 97.9%) 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% (Evaluation Criterion 1). In comparison, 88.8% of patients (95% CI: 84.6%, 91.8%) in the leuprolide group achieved and maintained sustained castration during the same period. The between-group difference was 7.9% (95% CI: 4.1%, 11.8%), demonstrating non-inferiority of relugolix to leuprolide as the lower bound of the 95% CI for the difference between groups was greater than the pre-specified non-inferiority margin of -10% (Evaluation Criterion 2) (p <0.0001; HR = 0.2321 [95% CI: 0.1489, 0.4613]).
- Results from three of the four sensitivity analyses were consistent with the primary analysis of the primary endpoint for sustained castration rate in the relugolix group (Evaluation Criterion 1). Per the rather conservative Sensitivity Analysis 3, the results were generally consistent with the primary analysis but did not meet Evaluation Criterion 1. All four sensitivity analyses demonstrated non-inferiority of relugolix compared with leuprolide (Evaluation Criterion 2).
- In virtually all subgroups, the result confirmed the results of the primary analysis of the primary endpoint, both for Evaluation Criterion 1 and 2.
- On Day 4, the castration rate was higher in the relugolix group compared with the leuprolide group, i.e. 56.04% (95% CI: 52.18, 59.97) vs 0% (95% CI: NE, NE), respectively (p < 0.0001).
- On Day 15, the castration rate was higher in the relugolix group compared with the leuprolide group, i.e. 98.71% (95% CI: 97.56, 99.39) vs 12.05% (95% CI: 8.88, 16.25), respectively (p < 0.0001).
- The proportion of patients with a > 50% reduction in PSA on Day 15 and confirmed at Day 29 was higher in the relugolix group compared with the leuprolide group, i.e. 79.4% (95% CI: 76.03, 82.53) vs 19.8% (95% CI: 15.50, 24.70), respectively (p < 0.0001).
- The rate of profound castration (< 20 ng/dL) on day 15 was higher in the relugolix group compared with the leuprolide group, i.e. 78.38% (95% CI: 75.06, 81.53) vs 0.98% (95% CI: 0.32, 3.00), respectively (p < 0.0001).
- The mean FSH level (SD) on day 169 was suppressed to a larger extent in the relugolix group compared with the leuprolide group, i.e. to 1.72 (1.376) IU/L vs 5.95 (3.071) IU/L, respectively (p < 0.0001).
- There was a trend (only) for a higher rate of testosterone recovery to > 280 ng/dL at 90 days after drug discontinuation in the relugolix group compared with the leuprolide group, i.e. 53.93% (95% CI: 45.20, 63.16) vs 3.23% (95% CI: 0.46, 20.77), respectively (*nominal* p = 0.0017).

3.3. Uncertainties and limitations about favourable effects

Both the primary endpoint as well as all secondary endpoints that were tested statistically are of pharmacodynamic nature or concern a biomarker, and are not clinical measures of patient benefit per se.

The Applicant has not provided a rationale for the sample size for the key secondary endpoint of testosterone recovery, nor any detailed information on how patients were selected for the subset to be followed for testosterone recovery. The latter could be a possible source of bias for this key secondary endpoint. These issues were not pursued, as this key secondary endpoint was not formally tested/analysed and was for exploratory purposes only.

3.4. Unfavourable effects

The most frequently reported **adverse events** for patients in the pivotal phase 3 study comparative trial versus the GnRH agonist leuprorelin were hot flush (54.3% on relugolix vs 51.6% on leuprolide) and fatigue (21.5% vs 18.5%). The frequencies for adverse events in ≥5% of patients were similar both on relugolix and on leuprolide, except for constipation (12.2% vs 9.7%), diarrhoea (12.2% vs 6.8%), arthralgia (12.1% vs 9.1%), and hypertension (7.9% vs 11.7%). All constipation and diarrhoea adverse events were mild or moderate, there were no serious adverse events of constipation or diarrhoea and median duration of both adverse events was similar.

In study 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. This imbalance for withdrawal is likely due to the fact that the study drug is given as a daily oral dose and the control leuprolide as a 3-month depot formulation.

In study MVT-601-3201, adverse events of hepatic transaminase elevation were reported for a slightly higher proportion of patients in the relugolix group compared with the leuprolide group (7.6% vs. 5.5%, respectively). However, ALT and AST values over time and a summary of hepatic laboratory abnormalities showed a similar profile of hepatic transaminases for both groups. No evidence of drug-induced liver injury was observed.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 58. Effects Table for Orgovyx (relugolix) for the Treatment of Adult Patients with Advanced Hormone-sensitive Prostate Cancer (data cut-off: 10 Dec-2019 [primary analysis])

Effect	Short Description	Unit	Relugolix	Leuprolide	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint						

Effect	Short Description	Unit	Relugolix	Leuprolide	Uncertainties/ Strength of evidence	References
Sustained castration rate	Cumulative probability of testosterone suppression to castrate levels of < 50 ng/dL while on study treatment from Day 29 through Day 337 (Evaluation Criterion 1)	% (95% CI)	96.7 (94.9, 97.9)	88.8 (84.6, 91.8)	**Strengths**: - Efficacy data derived from phase 3 RCT vs standard of care active comparator - Results of sensitivity and subgroup analyses support robustness of primary efficacy analysis of primary endpoint - Results of primary endpoint also supported by results of key secondary endpoints **Uncertainties**: - Primary endpoint and all key secondary endpoints in this table are of pharmacodynamic nature or concern a biomarker, and are not clinical measures of patient benefit *per se*	Clinical efficacy e.g. Table 16 and Figure **14**
	Difference from leuprolide at Day 337 (Evaluation Criterion 2)	% (95% CI)	7.9 4.1, 11.8			
			p <0.0001 Hazard ratio = 0.2621 (95% CI: 0.1489, 0.4613)			
Key secondary endpoints						
Castration rate on Day 4	Proportion of patients with testosterone < 50 ng/dL at Day 4	% (95% CI)	56.04 (52.18, 59.97)	0.00 (NE, NE)	See above for **Strengths** and **Uncertainties**	Clinical efficacy e.g. Figure **16** and Table 17
			p <0.0001			
Castration rate on Day 15	Proportion of patients with testosterone < 50 ng/dL at Day 15	% (95% CI)	98.71 (97.56, 99.39)	12.05 (8.88, 16.25)		
			p <0.0001			
PSA response on Day 15 through Day 29	Proportion of patients with a > 50% PSA reduction at Day 15 followed with confirmation at Day 29	% (95% CI)	79.4 (76.03, 82.53)	19.8 (15.50, 24.70)		Clinical efficacy e.g. Table 18
			p <0.0001			
Rate of profound castration on Day 15	Cumulative probability of testosterone suppression < 20 ng/dL on Day 15	% (95% CI)	78.38 (75.06, 81.53)	0.98 (0.32, 3.00)		Clinical efficacy e.g. Figure 17 and Table 19
			p <0.0001			
FSH level	Mean FSH level at Day 169	IU/L (SD)	1.72 (1.376)	5.95 (3.071)		Clinical efficacy e.g. Figure 18
			p <0.0001			
Testosterone recovery	Cumulative probability of testosterone recovery back to > 280 ng/dL at the 90-day follow-up[a]	% (95% CI)	53.93 (45.20, 63.16)	3.23 (0.46, 20.77)		Clinical efficacy e.g. Table 24
			nominal p = 0.0017[b]			
Unfavourable Effects						

Effect	Short Description	Unit	Relugolix	Leuprolide	Uncertainties/ Strength of evidence	References
Hot flush	Percentage of patients	%	54.3%	51.6%	Class effect of ADT Most common event	Clinical safety: Common Adverse Events
Constipation	Percentage of patients	%	12.2%	9.7%	Mild or moderate in severity. None were serious or led to study drug interruption or withdrawal.	
Diarrhoea	Percentage of patients	%	12.2%	6.8%		
Arthralgia	Percentage of patients	%	12.1%	9.1%		
Carbohydrate and lipid metabolic effects	Percentage of patients	%	8.5%	7.5%	Most events of diabetes mellitus were exacerbations of existing diabetes. The individual AEs do not favour one of the groups: 'Diabetes mellitus' 3.7% vs 1.9%; 'type II diabetes' 0.5% vs 1.9%	Clinical safety: Adverse events of special interest

Abbreviations: FSH = follicle-stimulating hormone; NE = not estimable; PSA = prostate-specific antigen; RCT = randomized controlled trial; AE = adverse event; IHD = ischemic heart disease; MACE = major cardiovascular adverse event; ADT = androgen deprivation therapy; MH = medical history
Notes:
[a] Time to testosterone recovery was assessed in a subset of 137 vs 47 patients.
[b] Time to testosterone recovery was performed at the primary analysis for exploratory purposes without formal testing. Testing order of time to testosterone recovery in the final analysis was to be preceded by castration resistance-free survival (see Table 10); however, the testosterone recovery analysis was not formally tested at the final analysis, because the results for castration resistance-free survival did not achieve statistical superiority.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The **pivotal study** met its primary endpoint, as treatment with relugolix resulted in a sustained castration rate of ≥ 90%, i.e. a testosterone level < 50 ng/dL from Day 29 through 337 (Evaluation Criterion 1), plus treatment with relugolix was noninferior to treatment with leuprolide as assessed by (this) sustained testosterone suppression rate (Evaluation Criterion 2). The results of the sensitivity and subgroup analyses are considered to support the robustness of the primary efficacy analysis of the primary endpoint. All key secondary endpoints tested hierarchically at the primary analysis, except for (time to) testosterone recovery, demonstrated superiority over/confirmed (at least) noninferiority to leuprolide. Achievement of castrate levels of testosterone is an acceptable primary efficacy endpoint in patients with hormone-sensitive advanced prostate cancer and is considered to meet the CHMP regulatory requirements (see Vantas Article 29(4) referral procedure [CHMP/247760/07] and EMA guidance [EMA/CHMP/703715/2012 Rev. 2]).

The results from the **supportive studies**, notwithstanding the slightly different relugolix dosages used and the fact that formal statistical testing was not conducted, can be considered to provide support for the activity of relugolix in lowering testosterone to castration levels in a sustainable manner, in patients with hormone-sensitive prostate cancer.

Safety data are primarily based on the pivotal phase 3 study MVT-601-3201, with a total of 298 patients who received oral relugolix 120 mg after an initial bolus of 360 mg for more than 48 weeks. The mean duration of relugolix use was 45.52 weeks. The documented safety exposure exceeds the requirements of ICH-E1 and is considered sufficient for adequate assessment of the safety profile of relugolix. Relugolix is well-tolerated since the majority of the AEs are mild to moderate in severity, and the discontinuations due to adverse events are low. Generally, the reported adverse events are in line with the safety profile of the comparator. No new safety issues or trends were identified in the safety data package provided. The potential risks and adverse drug reactions are sufficiently covered in the product information.

3.7.2. Balance of benefits and risks

In patients with androgen-sensitive advanced prostate cancer, treatment with relugolix resulted in adequate, sustained castration up to approximately one year of treatment duration, and demonstrated non-inferiority in terms of castration to standard of care treatment with leuprolide. Relugolix has been generally well-tolerated in most study patients with advanced prostate cancer. The most common adverse drug reactions are associated with low testosterone including hot flush, fatigue, and arthralgia. The potential risks of relugolix as a GnRH receptor antagonist are well known and include hepatic transaminase elevations, carbohydrate and lipid metabolic effects, adverse cardiovascular events, QT prolongation and mood disorders.

Based on the above, a positive benefit-risk balance can be concluded.

3.7.3. Additional considerations on the benefit-risk balance

The initially proposed indication was amended to adequately reflect the pivotal study population, i.e. patients with hormone-sensitive advanced prostate cancer, and be aligned with relevant precedents (Firmagon, Xtandi, Erleada, and Zytiga). Further, the data/results from study MVT-601-3201 are not considered sufficient proof of patient benefit beyond the hormone-sensitive prostate cancer setting and any indication beyond the hormone-sensitive prostate cancer setting would not be in line with EMA guidance and regulatory precedents.

3.8. Conclusions

The overall benefit/risk balance of Orgovyx is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Orgovyx is favourable in the following indication:

Orgovyx is indicated for the treatment of adult patients with advanced hormone-sensitive prostate cancer

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see SmPC section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.