NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Accord Healthcare:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Prostate Cancer UK
   b. Tackle Prostate Cancer – written by patient expert Dr. Stephen Allen

4. **Expert personal perspectives** from:
   a. Dr. Stephen Allen – Patient expert, nominated by Tackle Prostate Cancer
   b. Mr. Peter Rose – Patient expert, nominated by Prostate Cancer UK
   c. Prof. Jonathan Aning – Clinical expert, nominated by British Association of Urological Surgeons
   d. Dr. Amarnath Challapalli - Clinical expert, nominated by British Uro-Oncology Group

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre
   a. Addendum

6. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Document B

Company evidence submission

January 2024

File name	Version	Contains confidential information	Date
ID6187_Relugolix i. Company evidence submission [CON]	**1.0**	**Yes**	**24.01.24**

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Abbreviations

Acronym	Definition
ADT	Androgen Deprivation Therapy
AEs	Adverse Events
ALT	Alanine Aminotransferase
ARIs	Androgen Receptor Inhibitors
AST	Aspartate Aminotransferase
AUA	American Urological Association
BIC	Bayesian Information Criterion
BMJ	British Medical Journal
BNF	British National Formulary
BR	Biochemical Relapse
BSA	Body Surface Area
CAB	Combined Androgen Blockade
CEACs	Cost-effectiveness Acceptability Curves
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Intervals
CRFS	Castration Resistant-Free Survival
CRPC	Castration-Resistant Prostate Cancer
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CVA	Cerebrovascular accident
CVD	Cardiovascular Disease
DHPC	Direct Healthcare Professional Communication
DIC	Deviance Information Criterion
dL	Decilitre
DOC	Docetaxel
DSA	Deterministic Sensitivity Analysis
EAU	European Association of Urology
EBRT	External Beam Radiotherapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EMBASE	Excerpta Medica database
eMIT	Drugs and pharmaceutical Electronic Market Information Tool
ENZ	Enzalutamide

EOS	End of Study
EOT	End of Treatment
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FHS	Framingham Heart Study
FSH	Follicle-Stimulating Hormone
FU	Follow up
GEEs	Generalised Estimating Equations
GLM	Generalised Linear Model
GnRH	Gonadotrophin-Releasing Hormone
Hb	Haemoglobin
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HRU	Healthcare Resource Utility
HSPC	Hormone Sensitive Prostate Cancer
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ID	Identification
IHD	Ischemic Heart Disease
IPDs	Individual Participant Data
IQR	Interquartile Range
ITC	Indirect-Treatment Comparison
ITT	Intention-to-Treat
IU	International Units
IV	Intravenous
IWRS	Interactive Web Response System
kg	Kilogram
KM	Kaplan-Meier
KOL	Key Opinion Leader
LA	Locally Advanced
LH	Luteinizing Hormone
LHRH	Luteinizing Hormone Releasing Hormone
LYG	Life Years Gained
LYs	Life Years
MACE	Major Cardiovascular Events
MCM	Markov Cohort Model
MCMC	Markov chain Monte Carlo
mCRPC	Metastatic Castration Resistant Prostate Cancer

MedDRA	Medical Dictionary for Regulatory Activities
MEDLINE	Medical Literature Analysis and Retrieval System Online
MEs	Medication Errors
MFS	Metastatic Free Survival
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mHSPC	Metastatic Hormone Sensitive Prostate Cancer
MI	Myocardial Infarction
mITT	Modified Intent-to-Treat
mL	Millilitre
N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NE	Not Estimable
ng	Nanogram
NHB	Net Health Benefit
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NMB	Net Monetary Benefit
nmCRPC	non-metastatic Castration Resistant Prostate Cancer
OLE	Open Label Extension
ONS	Office for National Statistics
OR	Odds Ratio
OS	Overall Survival
OWSA	One-Way deterministic Sensitivity Analyses
PC	Prostate Cancer
PFS	Progression Free Survival
PICO	Patient/Population, Intervention, Comparators and Outcomes.
PRAC	Pharmacovigilance Risk Assessment Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance Status
PSA	Prostate-Specific Antigen
Q1	25th percentile
Q12W	Every 12 weeks
Q3	75th percentile
Q4W	Every 4 weeks
QA	Quality Assessment
QALY	Quality Adjusted Life Year
QD	Once Daily
QoL	Quality of Life
RCT	Randomised Controlled Trial

RP	Radical Prostatectomy
RR	Relative Risk
RT	Radiotherapy
RWE	Real World Evidence
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SF	Safety Follow-up
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SUCRA	Surface Under the Cumulative Ranking Curve
SWOG	Southwest Oncology Group
TA	Technology appraisal
TEAEs	Treatment Emergent Adverse Events
TIA	Transient Ischemic Attack
TS	Testosterone Suppression
ULN	Upper Limit of Normal
VAS	Visual Analogue Scores
WTP	Willingness To Pay

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with hormone-sensitive prostate cancer	People with hormone-sensitive prostate cancer	N/A
Intervention	Relugolix	Relugolix	N/A
Comparator(s)	Androgen deprivation therapy alone (including orchidectomy, GnRH agonists such as leuprorelin, goserelin, triptorelin, and buserelin, and GnRH antagonists such as degarelix)	Androgen deprivation therapy alone (including orchidectomy, GnRH agonists such as leuprorelin, goserelin, triptorelin, and buserelin, and GnRH antagonists such as degarelix)	N/A
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • prostate-specific antigen response	The outcome measures to be considered include: • overall survival • progression-free survival • response rate (testosterone suppression)	In addition to the outcomes listed, major cardiovascular events (MACE) are considered due to the risks of cardiovascular side effects in men commencing androgen deprivation therapy (ADT). Men with prostate cancer have a higher risk of cardiovascular (CV) and thromboembolic events and this risk increases with the use of GnRH receptor agonists (1-3). There is also evidence that the risk of major CV events is higher in men treated with GnRH agonists compared with GnRH antagonists or

	• time to prostate-specific antigen progression • adverse effects of treatment • health-related quality of life.	• prostate-specific antigen response • time to prostate-specific antigen progression • adverse effects of treatment • health-related quality of life. • Major cardiovascular events • testosterone recovery	bilateral orchidectomy (4, 5), particularly in men with pre-existing CV disease (6, 7). Additionally, testosterone recovery is considered as current ADT options are only available as injectable depot formulations, with testosterone suppression persisting months (up to two years) following discontinuation of treatment, prolonging safety concerns and symptoms associated with therapy (8). Testosterone deficiency is associated with metabolically adverse changes in body composition, increased insulin resistance, impaired bone health and hypogonadal symptoms, this inability to stop treatment rapidly with depot formulations is a major disadvantage.
Economic analysis		The economic analysis will be completed in the existing license subgroup of people with advanced hormone-sensitive prostate cancer (locally advanced or metastatic, including biochemical relapse).	There is not sufficient additional clinical data to support economic analysis in the pending license variation subgroups (see next row), as these patients comprise a subset of patients in the pivotal HERO study, for which no pre-specified analyses were conducted.
Subgroups to be considered	• People with advanced hormone-sensitive prostate cancer (high-risk localised, locally advanced or metastatic, including biochemical relapse) • People with high-risk localised or locally advanced hormone sensitive prostate cancer in combination with radiotherapy • People with high-risk localised or locally advanced hormone sensitive prostate cancer requiring neoadjuvant treatment prior to radiotherapy	• People with advanced hormone-sensitive prostate cancer (high-risk localised, locally advanced or metastatic, including biochemical relapse) • People with high-risk localised or locally advanced hormone sensitive prostate cancer	Accord have recently (December 28, 2023) received an approval from MHRA regarding the licence variation, which adds the second and third subgroups as stated to the previous population of advanced prostate cancer (metastatic, locally advanced and biochemical relapse [BR]). These additional subgroups are supported by the same dataset as the original license population, as these patients comprise a subset of patients in the

		in combination with radiotherapy • People with high-risk localised or locally advanced hormone sensitive prostate cancer requiring neoadjuvant treatment prior to radiotherapy	HERO study for which there were no pre-specified analyses. All available and relevant information in relation to these subgroups is included in section B.2. The systematic literature review (SLR) also does not include this subgroup of patients and the economic model is not currently structured to capture cost-effectiveness of relugolix in these subgroups. However, Accord believes the submission is appropriate to support the additional subgroups in the licence variation for the following reasons: 1. ADT as a pharmacological class (without specific mention of individual drugs) is recommended by the latest NICE, EAU, ESMO, and NCCN treatment guidelines and is used in routine practice as the mainstay of therapy in the aforementioned indications (high-risk localised and locally advanced prostate cancer). Current clinical practice and general perception assumes that there is equivalence amongst drugs in the ADT class. 2. Despite structural and mechanistic differences amongst medications, testosterone suppression constitutes the final common treatment goal whereby all GnRH receptor agonists and antagonists achieve their intended action and is a validated target in all such populations. 3. A cohort of patients with clinically advanced localised disease was included in the head-to-head study demonstrating noninferiority of relugolix vs leuprorelin in terms of sustained testosterone suppression (summarised in section B.2).

B.1.2. Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Relugolix (Orgovyx™)
Mechanism of action	Relugolix is a non-peptide gonadotrophin-releasing hormone (GnRH) receptor antagonist that competitively binds to the GnRH receptors in the anterior pituitary preventing native GnRH 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.
Marketing authorisation/CE mark status	Relugolix received an initial marketing authorisation from the European Medicines Agency on 29th April 2022 and UK Medicines Agency and Healthcare products Regulatory Agency (MHRA) on 17th June 2022. A licence variation to include all subgroups stated in the scope was granted on 28th December 2023
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Relugolix is a GnRH-receptor antagonist indicated: • for the treatment of adult patients with advanced, hormone-sensitive prostate cancer (high-risk localised, locally advanced, metastatic, including biochemical relapse) • for the treatment of high-risk localised and locally advanced hormone-sensitive prostate cancer (HSPC) in combination with radiotherapy. • As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced HSPC.
Method of administration and dosage	Treatment with relugolix 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.
Additional tests or investigations	None
List price and average cost of a course of treatment	The list price of relugolix is £150.16 per pack of 30 tablets. Based on the recommended dosage, the annual cost of treatment at list price would be up to £1826.95 (excluding loading dose). For non-metastatic patients, it is expected that patients will receive ADT for 2-years resulting in a cost of a course of treatment at list price of up to £3663.90 (including loading dose). For metastatic patients, it is expected that patients will receive ADT on average for 5-years resulting in an average cost of a treatment course of £9144.74 (including loading dose). This is based on a 5-year treatment window, as the 5-year survival rate is 26% to 30%.

Patient access scheme (if applicable)	Accord has submitted a patient access scheme and expects a decision in January 2024. [redacted]

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Prostate cancer epidemiology and risk factors

Prostate cancer is a malignant tumour of the prostate, a gland in the male reproductive system. It is the most common cancer in males in the UK, accounting for 52,000 new cases each year in the UK, (9) and over 12,000 deaths (9). While prostate cancer remains largely a disease diagnosed in men over the age of 65, testing (based on serum levels of prostate-specific antigen (PSA)) has increased the rate of diagnosis amongst men in their 40s and 50s (10)).

Family history, age and ethnicity are the most significant risk factors for clinically significant prostate cancer (10). Improvement in treatment and early diagnosis with PSA testing have resulted in fewer patients dying from prostate cancer (11). Overall, survival rates for localised disease are high (97%;(12)) but these rates decrease dramatically for advanced and metastatic disease, with a 5-year survival rate ranging from 26% to 30% (13). Cardiovascular disease (CVD) is the most common non cancer cause of death for men with prostate cancer (14-17). Patients with metastatic prostate cancer are at a significantly higher risk of CVD than men of the same age without prostate cancer (2, 18)

B.1.3.2. Clinical presentation, stage and prognosis

The clinical behaviour of prostate cancer ranges from an asymptomatic, well-differentiated tumour, that may never become clinically significant, to the clinically significant aggressive, high-grade cancer that causes metastasis, morbidity and death. At the time of diagnosis, 43% of patients have localised cancer (defined as tumour that remains within the prostatic capsule; stages T1-T2), 41% have locally advanced disease, defined as tumour that extends through the prostatic capsule (T3) or is fixed or invades adjacent structures other than seminal vesicles (T4), or disease with regional lymph node metastasis (N+) and 16% have distant metastases (19). Previously, prostate cancer was considered advanced when the disease had become metastatic (including non-regional lymph node metastasis) and was beyond curation. The definition has been expanded to encompass patients with significant

risk of disease progression and/or death, using stage, Gleason grade and PSA level e.g.

- locally advanced disease (stages T3-T4) and
- advanced localised disease (defined as T1 or T2 and PSA between 10 - 20ng/ml and Gleason 3+4 or Gleason grade 4+3).

Men whose disease progresses after radical treatment are similarly defined as having advanced prostate cancer. PSA or biochemical relapse represents the earliest indication of residual tumour (20). Approximately 40% of men who receive localized treatment will experience PSA relapse or rising PSA levels, and progress to advanced hormone-sensitive prostate cancer (advanced HSPC) (20).

B.1.3.3. Androgen deprivation therapy

Androgens are required for the normal growth and function of the prostate and almost all cancers (at an early stage) are dependent on androgens (androgen-sensitive). In 1941, Huggins and Hodges (21) observed that castration of men with prostate cancer halted tumour growth, and today, evidence-based treatment guidelines recommend androgen deprivation therapy (ADT) for the treatment of patients with advanced HSPC (22),(23),(24), (25).

In these guidelines, ADT is the foundation therapy to which other treatment options are added. NICE recommends ADT in combination with radiotherapy (RT) for intermediate-or high-risk localised disease and to manage patients with biochemical relapse if there is evidence of symptomatic local disease progression or any proven metastases or a PSA doubling time of less than 3 months. Where there is evidence of progression, ADT is usually continued upon development of metastatic prostate cancer. ADT is also recommended as first line treatment of metastatic HSPC, in combination with other medication, for example enzalutamide, docetaxel, etc. (22).

European Society for Medical Oncology (ESMO) guidelines similarly recommend ADT in combination with RT for high-risk localised, locally advanced disease and for men with biochemical relapse. ADT is recommended as first-line treatment of metastatic hormone naïve prostate cancer in combination with abiraterone/prednisone or apalutamide or enzalutamide or docetaxel (24).

Drugs within the ADT class are GnRH receptor agonists or antagonists and act by blocking the release of gonadotrophins by the pituitary. This in turn reduces the secretion of testosterone by the testes which means there are fewer circulating androgens available to bind and activate androgen receptors. GnRH is also known as luteinizing hormone releasing hormone (LHRH). GnRH agonists, such as leuprolide, goserelin, and triptorelin, are the most established and commonly used ADTs. The only GnRH receptor antagonist with National Institute for Health and Care Excellence (NICE) guidance that is currently accepted for use within NHS England is degarelix (Firmagon®), which is recommended as an option to treat adult male patients with advanced HSPC. Current ADT treatments are all injectable medicines that have limitations (see below).

Consistent with current clinical practice, drugs within the ADT class (GnRH agonists and antagonists) are considered equivalent (26) with respect to cancer-specific outcomes at all disease stages within the HSPC treatment pathway and are therefore used interchangeably. Despite structural and mechanistic differences amongst medications, testosterone suppression constitutes the final common treatment goal in such patients, whereby all GnRH receptor agonists and antagonists achieve this intended action. This is reflected in the regulatory labels of ADTs. Furthermore, a recent meta-analysis concluded that GnRH agonists and antagonists are equivalently efficacious against prostate cancer (27). Similarly, a published network meta-analysis (NMA) by Sari Motlagh et al. (28) showed that GnRH agonists relugolix and degarelix were clinically equivalent to each other, as well as to other ADTs. Current drugs in the ADT class have associated challenges, which are outlined in sections B.1.3.4 to B.1.3.7.

B.1.3.4. Clinical ‘flare’ and GnRH agonists

Prolonged activation of GnRH receptors by GnRH agonists lead to desensitization, and consequently to suppressed testosterone secretion (29). However, the initial overstimulation of pituitary receptors by GnRH agonists leads to a surge in testosterone (flare), lasting 1 to 3 weeks, that in some patients may exacerbate clinical symptoms leading to bone pain, spinal cord compression, pathological fractures, and bladder outflow obstruction (30). Estimated rates of clinical disease flare associated with GnRH receptor agonists range from 4% to 63% (31, 32). The

initial clinical flare of testosterone can be managed with simultaneous antiandrogen administration, such as bicalutamide (33), often called combined androgen blockade (CAB). However, the use of bicalutamide has been associated with hepatotoxicity (requiring monitoring of serum transaminase levels) and gynaecomastia (34).

GnRH antagonists block GnRH receptors directly, preventing native GnRH from binding to its receptors, and providing an alternative treatment approach without clinical flare for HSPC.

B.1.3.5. Cardiovascular events and GnRH receptor agonists

Although GnRH agonists are the mainstay of treatment in the UK, there are safety concerns associated with them. Men with prostate cancer have a higher risk of CV and thromboembolic events and this risk increases with the use of GnRH receptor agonists (1-3). There is evidence that the risk of major CV events is higher in men treated with GnRH agonists compared with GnRH antagonists or bilateral orchidectomy (4, 5), particularly in men with pre-existing CVD (6, 7, 16, 35). In 2010, the US Food and Drug Administration (FDA) issued a notification to add new safety warnings on GnRH agonist labels pertaining to the increased risk of diabetes, heart attack, sudden cardiac death, and stroke (36). Similar advisory statements were published by the American Cancer Society and American Urological Association (6).

Whilst the majority of studies demonstrate that the risk of CV events appears to be driven by GnRH receptor agonists, the PRONOUNCE study was the first randomized trial to prospectively compare a GnRH receptor agonist (leuprolide) to an antagonist (degarelix) with CV events as a primary outcome (37). It was terminated prematurely because of the smaller than planned number of participants and events, and no significant difference in CV events, at 1 year, between patients assigned to degarelix or leuprolide. The lower-than-expected enrolment was in part attributable to changes in the standard of care during the years of enrolment, including the addition of docetaxel or abiraterone to ADT for men with metastatic hormone-sensitive disease; confounding efforts to assess cardiac risks from either leuprolide or degarelix alone. Lastly, participants were required to have the ongoing care of a cardiologist, and many participants were treated for heart disease with drugs such as statins and beta blockers. This is likely to be the reason for having significantly lower MACE events

within the PRONOUNCE study. Unfortunately, continuous care of a cardiologist for all patients with prostate cancer is not reflected in current practice.

The only other prospective data supporting a MACE benefit is available from the HERO study, which assessed relugolix in comparison to leuprolide (38). The study results are included in section B.2.

Despite the relative lack of randomised evidence comparing the treatments, there is evidence to suggest that GnRH agonists are associated with higher risk of MACE than GnRH antagonists. In a meta-analysis of six randomized controlled trials (RCTs) (39), a significantly lower risk of cardiovascular events or mortality with the GnRH antagonist, degarelix compared with GnRH agonists, was observed in the total patient population (Hazard Ratio (HR): 0.6, 95% CI: 0.41-0.87, p = 0.008). No differences were observed in the incidence of either death or CV events amongst the men who had no baseline CVD. However, in those patients with pre-existing CV disease (*N* = 708), there were significantly fewer cardiac events or deaths experienced by patients receiving a GnRH antagonist (6.5%) compared with patients receiving GnRH agonists (14.7%).

Since this initial meta-analysis, several other studies have been published. Abufaraj et al. carried out a meta-analysis of 8 clinical trials in 20 published studies that showed GnRH antagonists are associated with fewer CV events than GnRH agonists (Relative Risk (RR):0.52, 95% CI 0.34–0.80) (27). Cirne et al., similarly demonstrated (in a meta-analysis of 10 randomized, controlled trials) that GnRH antagonists are associated with a significantly lower risk of adverse CV events, cardiovascular and all -cause mortality (40). The pooled risk ratios (95% confidence intervals; CI) among GnRH antagonist recipients for adverse CV events, cardiovascular death, and all-cause mortality were 0.57(0.390.81); 0.49(0.25–0.96); and 0.48(0.28–0.83), respectively(40). Lastly, a recent Cochrane Review (systematic literature review (SLR) and meta-analysis) reported that GnRH antagonists are associated with fewer CV events than GnRH agonists, both overall (RR: 0.66, 95% CI: 0.53-0.82, P<0.001) and when considering only randomised clinical trials (RR: 0.62, 95% CI: 0.43-0.89, P=0.01) or real-world data (RR: 0.68, 95% CI: 0.50-0.91, P=0.01) (41). In addition, GnRH antagonists were associated with lower

occurrences of cardiovascular death (60% risk reduction) and myocardial infarction (30% risk reduction) than GnRH agonists (41).

Specific to relugolix, a network meta-analysis of randomized trials comparing relugolix with degarelix showed that both GnRH antagonists were associated with lower CV event rates than GnRH agonists. Moreover, based on SUCRA (surface under the cumulative ranking curve) probability ranking analysis, it was highly likely that relugolix was better than degarelix and GnRH agonists in terms of a lower likelihood of 12-month CV events (28). Similarly, Cirne et al., found that the favourable effects of relugolix, as compared with a GnRH agonist, were consistent with those of degarelix. For example, in trials of relugolix, the pooled RR (95% CI) for CV events, CV death and overall mortality were respectively 0.56 (0.25–1.27), 0.40 (0.16–1.03), and 0.40 (0.16–1.03). In trials of degarelix, the pooled RR (95% CI) for cardiovascular events, cardiovascular death and overall mortality were respectively 0.52 (0.28–0.97), 0.61 (0.24–1.59), and 0.53 (0.27–1.04). Therefore, the existing evidence suggest that as a drug class, GnRH antagonists may offer advantages to GnRH agonists in the treatment of prostate cancer by reducing the risk of cardiovascular events and cardiovascular death (40).

B.1.3.6. Injection site reactions and issues with injections

Degarelix (Firmagon) is currently the only GnRH antagonist approved for the treatment of prostate cancer. Degarelix, administered by monthly 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 (42) and therefore does not require CAB. Use of degarelix in the clinical setting has been limited, possibly due to the rate of injection site reactions (44%) associated with monthly injections, which is significantly higher than with leuprolide (< 1%), which is administrated every 3 to 6 months (43). Degarelix also requires a large injection volume (4 mL) compared with leuprolide (0.375 mL for the 22.5 mg 3-month depot injection) (44).

Although the risk of injection site reactions is lower with GnRH agonists, they are still regarded as occurring at a frequency of either very common or common (45, 46). There have also been reports of medication errors (MEs) leading to lack of efficacy associated with leuprorelin-containing depot medicinal products, albeit with different

reporting rates per formulation (European Medicines Agency, EMA/397961/2020) (47). The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommended measures to avoid handling errors in the preparation and administration of leuprorelin depot medicines. The review found that handling errors resulted in some patients receiving insufficient amounts of their medicine. As a result of this review, a direct healthcare professional communication (DHPC) was sent to inform that handling errors with depot preparations of leuprorelin medicines could result in underdosing and a lack of efficacy. The committee also recommended that only healthcare professionals familiar with the preparation steps for leuprorelin depot medicines should prepare and administer the medicines to patients.

B.1.3.7. Slow recovery of testosterone after discontinuation of treatment

As mentioned, current ADT options, including GnRH receptor agonists and degarelix (antagonist), 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 (8, 48). Persistently low testosterone concentrations are associated with a wide variety of adverse effects (including increased insulin resistance, impaired bone health and hypogonadal symptoms (48)) and this inability to stop treatment rapidly with depot formulations is a major disadvantage.

B.1.3.8. About the product: Relugolix

Current standard of care treatment with GnRH receptor agonists has known limitations. These include:

- An initial surge in testosterone with risk of clinical flare
- Increased risk of CV events
- Injections site reactions
- Slow recovery of testosterone after discontinuation of treatment.

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
- Slow recovery of testosterone after discontinuation of treatment.

In England, the use of degarelix is also limited to patients with spinal metastases (26).

Relugolix (previously known as TAK-385, T-1331285, RVT-601 and MVT-601) is the first oral, non-peptide, GnRH receptor antagonist. Relugolix acts by competitively binding to GnRH receptors in the anterior pituitary, preventing endogenous GnRH from binding, thus inhibiting signalling and subsequent secretion of LH and FSH. Consequently, the production of testosterone from the testes is reduced. Relugolix does not cause an initial surge in testosterone associated with the GnRH agonists which may lead to worsening of prostate cancer symptoms in some cases (e.g., bulky disease or in patients with impending clinical complications such as bone pain, acute bladder outlet obstruction, obstructive renal failure, or spinal cord compression).

The initial regulatory approval of relugolix in advanced HSPC followed a favourable opinion by the Committee for Medicinal Products for Human Use (CHMP) of the EMA (procedure EMEA/H/C/005353/0000 in February 2022) and by MHRA (PLGB 55917/0001 in June 2022 and December 2023.

A licence variation has been recently approved by the MHRA in December 2023, and the current marketing authorisation in this indication therefore covers the following groups:

- For the treatment of adult patients with advanced hormone-sensitive prostate cancer (initial licensed indication).
- For the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy (approved in recent variation submission).

- As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer (approved in recent variation submission).

Clinically, relugolix is recommended in the recent update of the ESMO Clinical Practise Guidelines for prostate cancer with an ESMO Magnitude of Clinical Benefit Score of 4. For non-curative indications, a score of 4 indicates reduced toxicity or improved quality of life (QoL) with evidence for statistical non-inferiority or superiority in progression-free survival/overall survival. [redacted]

Relugolix fulfils an unmet need for an improved, oral treatment option for advanced hormone-sensitive prostate cancer with the following benefits:

- A once daily, oral treatment option with significantly lower resource use than its comparators, that all require subcutaneous (SC) administration by a nurse, eliminating the need for nurse administration, associated indirect costs (such as patient transport and time off work), injection-site reactions and pain of currently available ADTs (49).

- No initial testosterone surge associated with GnRH agonists, eliminating the need for a lead-in antiandrogen to counteract potential testosterone flare induced with LHRH agonists. This reduces burden on both patients and healthcare providers.

- A unique advantage of a fast testosterone recovery if the patient needs to discontinue treatment (38) because of intolerance or treatment-related side effects.

To understand and qualitatively (19 patients) and quantitively (48 patients) evaluate the experience of ADT in prostate cancer patients, a two-section survey was conducted in the UK between July to September, 2023 (data on file, (50)). Patients were recruited via a Patient Support Charity. Patients had mainly locally advanced

and metastatic prostate cancers (PC), and most of them were on ADT for more than 6 months or had previously received ADT.

Patients shared that different factors affect their experience with ADT, such as adverse events (some of them persisting months after treatment cessation) and variable NHS services and organising ADT injections can be inconvenient and stressful for some patients. Although time to travel and pain related to injections are generally accepted by patients as almost inevitable, they indicated a need for more involvement in their ADT treatment decisions.

The second section involved an anchored MaxDiff methodology to capture the most and least preferred from a list of 11 attributes of ADT, and a treatment preference exercise to understand the preferred choice of patients when proposed different therapeutic options as 5 blinded treatment profiles. 63% of patients chose relugolix as the preferred ADT when presented the blinded treatment options. The most common reason for selecting relugolix was oral administration, followed by speed of testosterone recovery and least impact on their daily lives.

One of the biggest concerns for patients was the anxiety/stress that they undergo when booking an appointment for their next injection as the responsibility is on the patient. The results from this study are planned to be published in Q3/4 2024.

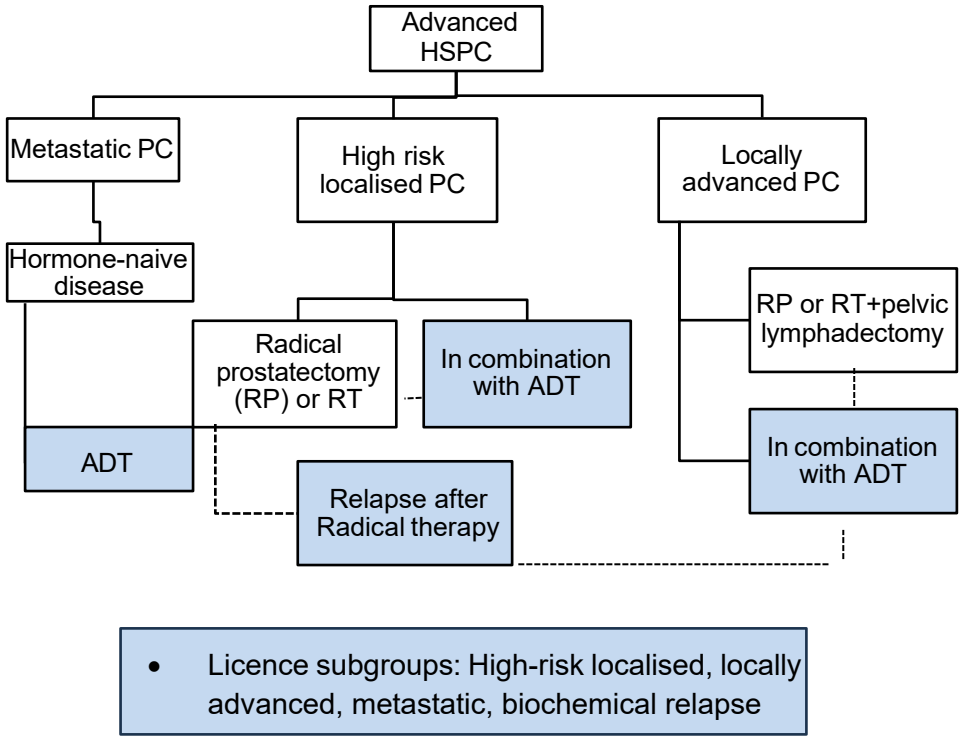
B.1.3.9. Place in therapy in England

As stated, the approved indication is:

- For the treatment of adult patients with advanced hormone-sensitive prostate cancer.
- For the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy.
- As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer.

The clinical care pathway for advanced hormone-sensitive prostate cancer (including the subgroups mentioned in the license, is shown in Figure 1. Blue boxes denote where relugolix would be positioned within the current pathway.

Figure 1: NICE pathway for the management of advanced HSPC prostate cancer



Relugolix is indicated (highlighted in blue) for patients with, high-risk localised, locally advanced, metastatic hormone-sensitive disease who would otherwise have ADT. Relugolix is also indicated for patients who relapse after radical treatment (broken line). Adapted from NICE treatment recommendations for advanced prostate cancer (NG131) (51) and ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (52).

HSPC = Hormone-sensitive prostate cancer, ADT = androgen deprivation therapy, RP = radical prostatectomy, RT = radiotherapy

B.1.4. Equality considerations

Accord does not believe that there are equality considerations that are likely to impact the recommendations and their appropriateness.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

Appendix D: Identification, selection and synthesis of clinical evidence contains full details of the process and methods used to identify and select the clinical evidence relevant to relugolix for the treatment of advanced prostate cancer.

In summary, a total of 54 publications consisting of 38 unique trials were identified by SLR, extracted and assessed for methodological quality. Treatment comparisons from each study identified by the SLR were bucketed into 2 categories: ADT of interest vs ADT of interest and ADT of interest vs other therapy.

- Seven unique trials evaluated ADT vs ADT as specified in the interventions of interest in the PICO (Appendix D: Identification, selection and synthesis of clinical evidence)
- An additional 24 trials evaluating ADT vs another ADT or *other* therapies were also included because they had the potential to facilitate indirect treatment comparisons in this target population (section B.2.9)
- Seven unique trials evaluated ADT as an open label extension.

Of the seven unique trials evaluating ADT vs ADT as specified in the PICO (Patient/Population, Intervention, Comparators and Outcomes), two studies presented evidence for relugolix:

- CTgov 2018/ NCT02083185 – locally advanced or metastatic disease
- HERO/ NCT03085095°- advanced disease

The single phase 3 study, known as MVT-601-3201 or the HERO trial (NCT03085095), is presented in section B.2.2.

In addition, there is one further phase 2 trial of interest, which was excluded from the SLR as the population included patients that do not have advanced prostate cancer (53). This trial compared relugolix and degarelix. Given that both products are GnRH antagonists, and that degarelix is the only ADT that has previously undergone NICE appraisal, the trial is presented in section B.2.2.

B.2.2. List of relevant clinical effectiveness evidence

B.2.2.1. Evidence base for relugolix

The efficacy and safety of relugolix in HSPC has been demonstrated through a single multinational Phase 3 randomized, open-label trial (HERO/NCT03085095), two phase 2 studies (C27002/NCT02083185 (54, 55)) and C27003/NCT02135445 (53)) and two phase 1 studies (TB-AK160108/NCT02141659 (56) and C27001/ EudraCT Number 2011-002868-24).

In addition to the above, there are two other sources of evidence for relugolix that have not been sponsored by Accord:

- Apa-RP study: a single-arm, open label, multicentre, phase II study evaluating the biochemical recurrence-free rate in patients with high-risk localised prostate cancer following radical prostatectomy who receive apalutamide with ADT.

- Retrospective study evaluating patient's compliance on relugolix: A retrospective study of patients treated with relugolix in the United States undertaken to evaluate compliance and efficacy in a real-world setting.

These studies, as well as phase 1 and 2 trials not included in the main body of the submission, are summarised briefly in Appendix D: Identification, selection and synthesis of clinical evidence (Other studies of relugolix).

B.2.2.1.1. Study C27003

Study C27003 (NCT002135445) (53) was not used to populate the economic model but is included in sections 2.2 to 2.6. The trial was published in European Urology (53). As stated previously, this trial compared two GnRH antagonists (relugolix and degarelix). The results of this study support the phase 3 pivotal study as the primary endpoint used the same surrogate marker. This study was not included in the SLR, NMA or economic model because the patient population was not within the currently licenced indication, which is advanced HSPC. However, data in the neoadjuvant/adjuvant radiotherapy setting is presented briefly because the data support the efficacy of relugolix in combination with radiation therapy in the

marketing authorisation application. A summary of Study C27003 is presented in Table 3.

Table 3: Clinical effectiveness evidence from Study C27003

Study	C27003/NCT02135445, Dearnaley 2020
Study design	Phase 2, randomised, open-label, parallel-group efficacy and safety trial
Population	Males, aged 18 years or older with a histologically confirmed diagnosis of localized prostate adenocarcinoma of intermediate risk for which 6-month neoadjuvant and adjuvant ADT to external beam radiotherapy (EBRT) was indicated. High-risk patients were also considered for inclusion if, based on physician judgement, they were deemed likely to benefit from 6 months of ADT
Intervention(s)	Relugolix 320 mg on Day 1 then 120 mg QD for 24 weeks
Comparator(s)	Degarelix 4-week depot injection, 320 mg on Day 1 then 80 mg Q4W for 24 weeks.
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No
Rationale if study not used in model	The study includes supporting data on the clinical effectiveness of relugolix in HSPC. However, it was not conducted within the indication explored in the model, which is advanced HSPC.
Reported outcomes specified in the decision problem	Testosterone suppression to castrate levels PSA response Testosterone recovery Health-related quality of life Adverse effects of treatment
All other reported outcomes	Profound castration rate (< 20 ng/dL) FSH levels LH levels

B.2.2.1.2. HERO trial

Table 4 summarises the pivotal HERO trial, the results of which have been published in the New England Journal of Medicine (38) and for a subgroup of patients receiving combination therapy, published in Clinical Genitourinary Cancer (57).

Table 4: Clinical effectiveness evidence from the HERO trial

Study	HERO (MVT-601-3201, NCT03085095), Shore 2020
Study design	*Phase 3, randomised, open-label, parallel-group efficacy and safety trial*
Population	Males aged 18 years or older with androgen-sensitive advanced prostate cancer who are candidates for at least 1 year of continuous ADT. Eligible patients could have one of three clinical disease presentations: evidence of biochemical (PSA) or clinical relapse after local primary intervention with curative intent, newly diagnosed hormone-sensitive metastatic disease, or advanced localized disease unlikely to be cured by local primary intervention with curative intent.
Intervention(s)	Relugolix 360 mg on Day 1 then 120 mg QD for 48 weeks
Comparator(s)	Leuprolide 3-month depot injection, 22.5 mg (or 11.25 mg in Japan, Taiwan and China) every 12 weeks for 48 weeks
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	**Time to PSA progression** **Overall survival** Progression free survival PSA response Response rate Adverse effects of treatment (**including major cardiovascular events (MACE).** **Health-related quality of life**
All other reported outcomes	**Testosterone suppression to castrate levels (< 50 ng/dL)** Testosterone recovery Sustained profound castration rate (to < 20 ng/dL) FSH levels Castration resistance-free survival **Treatment emergent adverse effects**

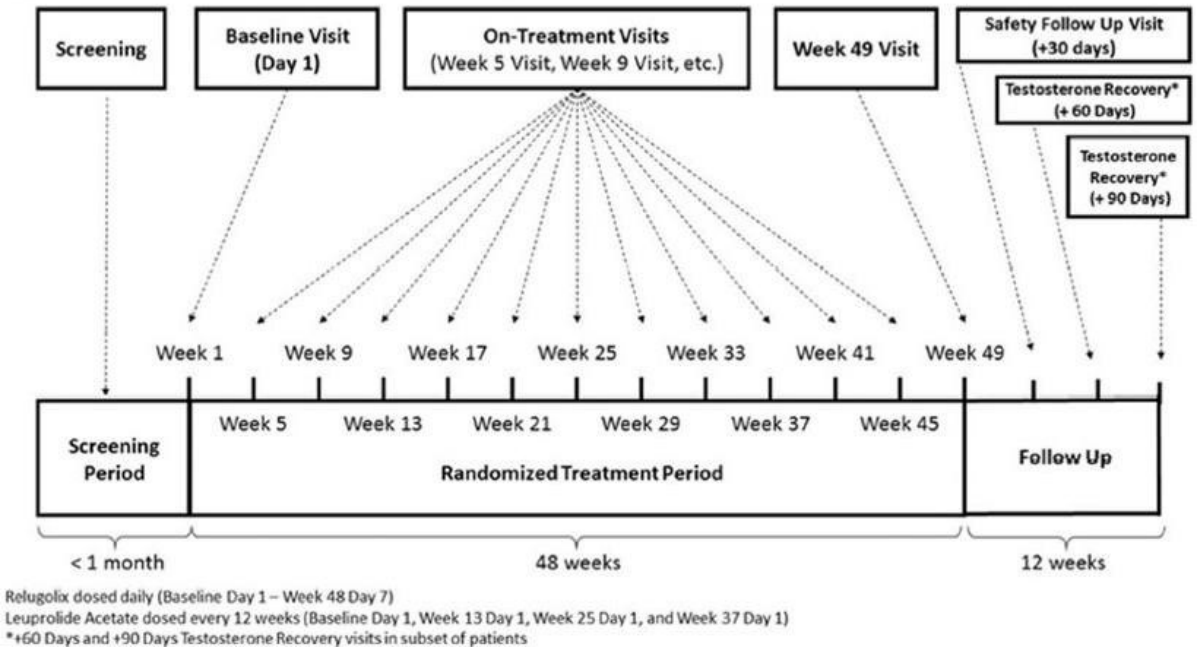
B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. Methodology

B.2.3.1.1. HERO trial design

HERO is a pivotal multinational Phase 3, randomized, open-label, parallel group efficacy and safety trial conducted between April 2017 and December 2018. The objective was to evaluate the safety and efficacy of oral relugolix compared to leuprolide in patients with androgen sensitive advanced prostate cancer who required at least 1 year of continuous ADT. 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 up to 90 days to assess testosterone recovery. A schematic of the overall study design is shown in Figure 2.

Figure 2: HERO study design schematic



The target population focused on men aged 18 or older diagnosed with androgen-sensitive advanced prostate cancer who were candidates for at least 1 year of continuous ADT for the management of androgen-sensitive advanced prostate cancer and who were not candidates for surgical or radiation therapy with curative intent. Patients previously treated with taxanes or expected to receive taxanes after

initiation of ADT were excluded, as were patients receiving ADT adjuvant or neoadjuvant to radiotherapy as primary definitive therapy.

The key inclusion and exclusion criteria for HERO are described in Table 5.

Primarily, patients were enrolled at 160 centres globally, including North and South America, Europe, and Asia Pacific region, and randomly assigned, in a 2:1 ratio, by means of an interactive web response system (IWRS). to receive either relugolix (120 mg once daily after a single oral loading dose of 360 mg) or leuprolide acetate (22.5 mg [or 11.25 mg in Japan and Taiwan] by injection every 3 months) for 48 weeks. 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. Randomization was stratified according to geographic region (North and South America, Europe, and Asia-Pacific region), the presence or absence of metastatic disease, and age (≤75 and >75 years). Trial visits occurred at baseline and every 4 weeks for 48 weeks.

Blinding was not applicable, however some data access restrictions intended to minimize bias were put in place (section B.2.5.1). 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.

The primary outcome in the HERO trial was sustained castration rate defined as the cumulative probability of testosterone suppression to < 50 ng/dL from week 5, Day 1 (Day 29) through Week 49, Day 1 (Day 337). A full list of outcomes from the HERO trial is presented in section B.2.3.1.

A comparative summary of trial methodology for the HERO trial and Study C27003 is presented in Table 6.

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Table 5: Key eligibility criteria for HERO

Inclusion	Exclusion
Males, aged ≥18 years old with a histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate	In the investigator's opinion, was likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating ADT
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;	Had previously received a GnRH analogue 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 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 jaundice or known current active liver disease from any cause
Had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.	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 electrocardiogram (ECG) abnormalities
	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

B.2.3.1.2. Study C27003 trial design

Study C27003 was a phase 2 randomised, open-label, parallel-group study conducted between June 2014 and December 2015. The trial was not blinded. Patients were randomised in a 3:2 ratio to receive 24 weeks of either oral relugolix (loading dose of 320 mg on day 1 and 120 mg daily thereafter) or degarelix as a subcutaneous depot injection (loading dose of 240 mg on day 1, and then 80 mg every 4 weeks). Patients were randomised sequentially by study centre. No stratification was implemented in the computer-generated randomisation schedule. Unique randomisation numbers were assigned to patients using a centralised interactive voice/ web response system. The inclusion of degarelix provided a contemporary GnRH antagonist benchmark for relugolix, using the same assays and assessments. EBRT was initiated after 12–16 weeks of ADT, as per each clinical site's standard of care.

The protocol did not specify the use of adjunctive medications such as calcium and vitamin D, but these could have been given at the clinician's discretion.

Patients were evaluated on days 1, 2, and 4 during week 1; once in each of weeks 2, 3, and 5; every 4 weeks thereafter during the 24-week treatment period; and for 12 weeks after treatment discontinuation. A schematic of the trial design is shown in Figure 3.

Eligible male patients were aged ≥18 years with a histologically confirmed diagnosis of localised, intermediate-risk prostate cancer, for whom 6-month neoadjuvant and adjuvant ADT to EBRT was indicated. High-risk patients were also considered for inclusion if, based on physician judgement, they were deemed likely to benefit from 6 months of ADT. The criteria for establishing intermediate-risk prostate cancer included the presence of one of the following, without any high-risk feature: T2b–T2c disease, Gleason score 7, or PSA 10–20 µg/L. Additional inclusion criteria included: EBRT scheduled to begin ≥12 weeks after baseline visit; screening serum testosterone >5.2 nmol/L (150 ng/dL); screening PSA concentration >2 µg/L; body mass index ≥18.0 at screening or baseline; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening. Based on investigator discretion and clinical assessment of the patient's overall medical and disease status,

participation was allowed for older patients with high-risk disease (e.g., based on Gleason score or tumour status) who were deemed likely to benefit from 6 months of neoadjuvant/adjuvant ADT.

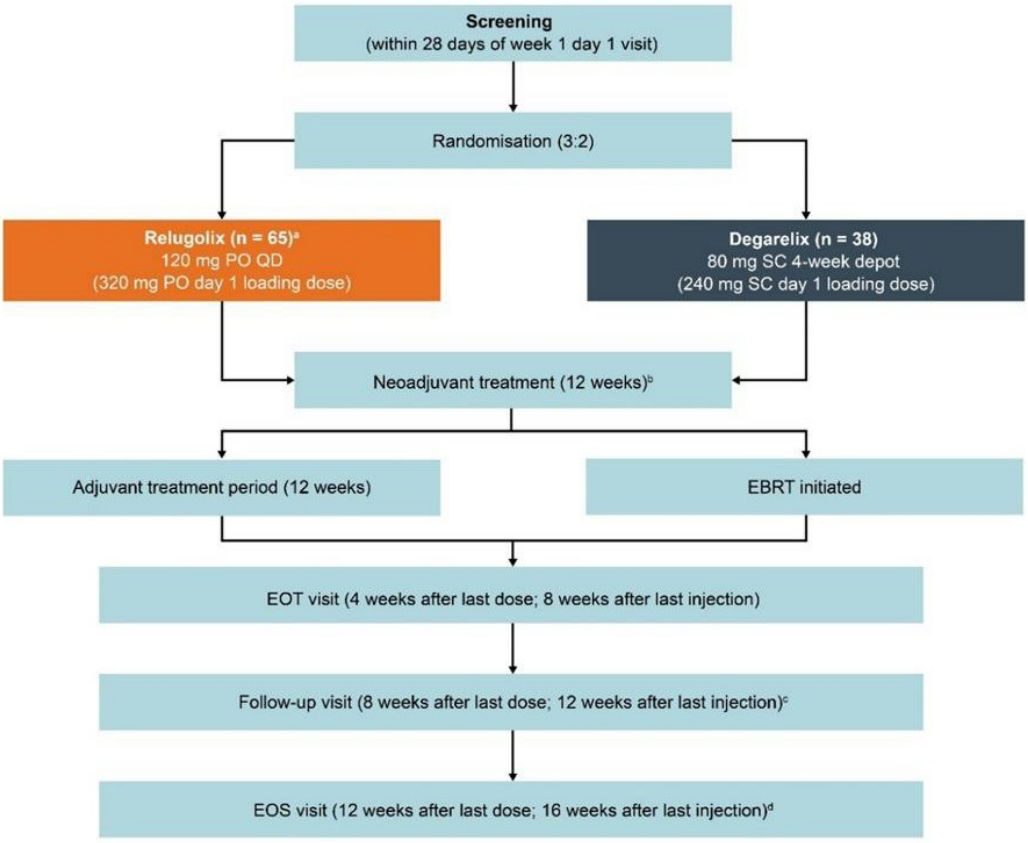
Patients were excluded if they had prior or current use of a GnRH analogue or androgen receptor antagonist as first-line hormone therapy (unless total treatment duration was <6 months and was completed ≥1 year prior to planned baseline visit), history of another malignancy in the 2 years prior to first dose of study drug, or previous malignancy with evidence of residual disease.

Additional exclusion criteria included: clinically significant underlying disease, based on abnormal screening laboratory values (alanine aminotransferase and/or aspartate aminotransferase >1.5x upper limit of the normal [ULN] range); serum creatinine >2.0 mg/dL; total bilirubin >2.0x ULN; uncontrolled diabetes (Hb A1c >10%) or previously undiagnosed diabetes mellitus with Hb A1c >8%; history of significant cardiac condition ≤6 months before administration of first dose of study drug, electrocardiogram abnormalities, congenital long QT syndrome, uncontrolled hypertension (despite medical therapy), or current use of Class IA or Class III antiarrhythmic medications; treatment with any investigational products ≤3 months before the first dose of study drug; known, previously diagnosed human immunodeficiency virus infection, active chronic hepatitis B or C, life-threatening illness unrelated to prostate cancer, or any other serious illness that has the potential to interfere with study participation; known gastrointestinal disease or procedure that could interfere with the oral absorption or tolerance of relugolix; and admission or evidence of substance (alcohol/drug) abuse.

The primary outcome of Study C27003 was rate of effective castration defined as the estimated proportion of patients with testosterone concentrations <1.73 nmol/l (<50 ng/dl) at all scheduled visits. A full list of outcomes from Study C27003 are presented in section B.2.3.1.

A comparatiove summary of trial methodology for the HERO trial and Study C27003 is presented in Table 6.

Figure 3: C27003 study design schematic



ADT=androgen deprivation therapy; EBRT=external beam radiation therapy; EOS=end of study; EOT=end of treatment; PO=orally; QD=once daily; SC=subcutaneous. Note: Week 21 Day 1 is the last study day scheduled for depot injection. [a] Relugolix was administered orally QD 30 minutes before breakfast. [b] Patients received ADT for at least 12 weeks before starting EBRT, and EBRT started no later than 16 weeks.[c] Patients who did not complete 12 weeks of study treatment did not participate in the follow-up visit. [d] The EOS visit occurred earlier for patients who did not complete 12 weeks of study treatment. Adverse events, serious adverse events, and concomitant medications continued to be collected and recorded through 30 days after the last dose of relugolix or 4 weeks plus 30 days after the last degarelix injection.

B.2.3.1. Comparative summary of trial methodology

A comparative summary of trial methodology for the HERO trial and Study C27003 is presented in Table 6.

Table 6: Comparative summary of trial methodology

Trial number (acronym)	NCT03085095/MVT-601-3201 (HERO)	NCT02135445 (C27003)
Location	160 centres globally, including North and South America, Europe, and Asia Pacific region	23 centres in the US (18 sites) and UK five sites).
Trial design	Phase 3 randomised, open-label, parallel group study	Phase 2 randomised, open-label, parallel-group study
Eligibility criteria for participants	Males aged 18 years or older with androgen-sensitive advanced prostate cancer who were candidates for at least 1 year of continuous ADT and who were not candidates for surgical or radiation therapy with curative intent.	Males aged 18 years or older with a histologically confirmed diagnosis of localized prostate adenocarcinoma of intermediate risk for which 6-month neoadjuvant and adjuvant ADT to EBRT was indicated. High-risk patients were also considered for inclusion if, based on physician judgement, they were deemed likely to benefit from 6 months of ADT
Settings and locations where the data were collected	Australia, Japan, Republic of Korea, New Zealand, Taiwan, Austria, Belgium, Germany, Denmark, Spain, Finland, France, UK, Italy, Netherlands, Poland, Slovakia, Sweden, Brazil, Canada, USA,	UK and USA
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	Participants were randomly assigned in a 2:1 ratio to receive relugolix (n= 624 , 360 mg on Day 1 then 120 mg QD) for 48 weeks or leuprolide (n= 310, 22.5 mg (or 11.25 mg in Japan, Taiwan, and China) 3M depot injections for 48 weeks.	Participants were randomly assigned in a 3:2 ratio to receive relugolix (n = 65, 320 mg on Day 1 then 120 mg QD) for 24 weeks or degarelix (n = 38, 320 mg on Day 1 then 80 mg Q4W depot for 24 weeks.
Permitted and disallowed concomitant medication	Permitted medications: Antiandrogens (e.g., bicalutamide, flutamide, nilutamide) for the first 4 weeks or longer if indicated, as determined by the investigator for the management of flare. In the event of disease progression despite castration, patients were allowed add-on treatment with either enzalutamide or docetaxel.	Permitted medications: None listed Prohibited medications: GnRH analogues or androgen receptor antagonists (1 yr prior to the first dose of study medication until the end of treatment visit and the completion of all study activities). amiodarone (6 months before day 1 through completion of all study activities). Nutraceuticals (e.g., St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin), start of

	Prohibited medications (prior to the first dose of study medication until the end of treatment visit and the follow-up period was complete): GnRH analogues; GnRH receptor antagonists; antiandrogens; CYP17 inhibitors; other androgen suppressing agents or androgens; 5 alpha 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.	screening period through completion of the study. Intake of known over-the counter moderate and strong inhibitors/inducers of cytochrome P450 enzymes 3A4/5 (including the inhibitor amiodarone) or P-glycoprotein inhibitors (including diltiazem), 14 days before day 1 through completion of all study activities, in patients randomized to relugolix.
Primary outcomes (including scoring methods and timings of assessments)	Sustained castration rate defined as the cumulative probability of testosterone suppression to < 50 ng/dL from week 5, Day 1 (Day 29) through Week 49, Day 1 (Day 337). To determine whether the sustained castration rate is ≥ 90% • Evaluation criterion 1 (FDA): to determine whether the sustained castration rate is ≥ 90%. • Evaluation criterion 2 (EMA): To establish the noninferiority of relugolix compared with leuprolide 3M depot injection as assessed by the cumulative probability of sustained testosterone suppression. The lower bound of the 95% CI 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.	Rate of effective castration, between 4 weeks and 24 weeks of treatment, defined as the estimated proportion of patients with testosterone concentrations <1.73 nmol/l (<50 ng/dl) at all scheduled visits.
Other outcomes used in the economic model/specified in the scope	Outcomes in the model: • Sustained castration rate • Time to PSA progression • Adverse events e.g., MACE Other outcomes specified in the scope: • Testosterone suppression to <50 ng/dL • PSA response • Profound castration rate (<20 ng/dL) • FSH level • Castration resistant -free survival (CRFS) • Testosterone recovery	Outcomes in the model: • N/A Other outcomes specified in the scope: • Profound castration rate (<20 ng/dL) • PSA response • Quality of life • Adverse events

	• Sustained profound castration rate • Adverse events • Overall survival • Quality of life	
Pre-planned subgroups	Subgroup analyses were conducted for geographic region, age, race, ethnicity, baseline testosterone and PSA levels, clinical disease state at screening, Gleason score, and the presence of metastatic disease. Subgroup analyses were conducted for sustained castration rate and noninferiority of relugolix compared with leuprolide. Castration resistance-free survival was assessed in the subgroup of metastatic patients and the extended intention-to-treat (ITT) population (approximately 1100 patients randomized). A pre-specified post hoc analysis of the incidence of cardiovascular events in patients with or without a reported medical history of adverse cardiovascular events (patients with and without MACE) was also performed.	N/A

Note: For the HERO trial, 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. EBRT = external beam radiotherapy; ADT = androgen deprivation therapy

B.2.3.2. Trial baseline characteristics

B.2.3.2.1. HERO baseline characteristics

The demographic characteristics of patients in the mITT population are shown in Table 7. Overall, demographics were similar between the treatment groups. The predominant racial representation in the study was white (68.4% overall, with similar proportions in both groups). The mean age for all patients in the study was 71.7 (standard deviation [SD] = 7.84) years overall with similar mean ages between treatment groups. The proportion of patients enrolled from Europe was 39.7% (including 1.1% from the UK from four study sites), 28.9% from North America, 21.0% from Asia, 5.7% from South America and 4.7% from rest of world.

Table 7: Demographic characteristics of participants in HERO across treatment groups (mITT Population)

(HERO) Baseline characteristic	**Relugolix**	**Leuprolide**	**Total**
	(n= 622)	(n=308)	(n=930)
Age category			
≤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%)
UK	8 (1.3%)	2 (0.6%)	10 (1.1%)
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; The Intent-To-Treat (ITT) population consists of all patients randomized to treatment who had taken at least one dose of study treatment. 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

Disease-specific baseline characteristics in the modified intent-to-treat (mITT) population are presented in Table 8 and were similar between the treatment groups and representative of the intended target population for this study as well as for patients with advanced prostate cancer in general. Approximately half (50.2%) of the men enrolled had biochemical recurrence after definitive treatment for prostate cancer; approximately one third (27.1%) had advanced localised disease and 22.7% had newly diagnosed androgen-sensitive metastatic disease at the time of enrolment. The mean PSA level at baseline was higher in the relugolix group (104.2 ng/mL) than in the leuprolide group (68.6 ng/mL); the median PSA values were similar in the two groups (11.7 and 9.4 ng/mL, respectively). More than 90% of the patients had at least one cardiovascular risk factor across the three main categories assessed, which included lifestyle risk factors such as tobacco use and obesity, cardiovascular risk factors such as diabetes and hypertension, and a history of a major adverse cardiovascular event. The percentage of patients with these risk factors was similar in the two treatment groups. Treatment adherence (defined as the percentage of expected doses actually taken) was more than 99% in both groups. In the relugolix group, 90.2% of the patients completed 48 weeks of treatment, as compared with 89.0% in the leuprolide group. The median follow-up time in both groups, including the 30-day safety follow-up period for adverse events, was 52 weeks.

Table 8: Disease-specific characteristics of participants in HERO (mITT population)

(HERO) **Baseline characteristic**	**Relugolix**	**Leuprolide**	**Total**
	(n=622)	(n=308)	(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%)
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%)
PSA (ng/mL)			
Mean (SD)	104.15 (415.96)	68.55 (244.04)	92.36 (368.26)
Median	11.69	9.43	10.84
Testosterone (ng/dL)			
n	612	300	912
Mean (SD)	436.07 (158.98)	409.95 (149.07)	427.48 (156.19)
Median	415.76	395.91	407.60

FSH level -IU/litre [d] Mean (SD)	16.3 (12.8)	16.7 (14.5)	16.4 (13.4)
Cardiovascular risk factors – n (%) [e] Lifestyle risk factors [f] Cardiovascular or cerebrovascular risk factors [g] History of MACE [h]	570 (91.6) 422 (67.8) 488 (78.5) 84 (13.5)	290 (94.2) 202 (65.6) 254 (82.5) 45 (14.6)	860 (92.5) 624 (67.1) 742 (79.8) 129 (13.9)

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.[d] The normal range of FSH values for adults is 1.5 to 12.4 IU per litre. [e] Patients with multiple risk factors were counted only once. [f] Lifestyle risk factors included tobacco smoking (current or past), heavy alcohol use, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 30. [g] Cardiovascular or cerebrovascular risk factors included prespecified event terms in the MACE query and a manual search of known risk factors, including hypertension; dyslipidaemia; diabetes; a history of myocardial infarction or cardiovascular disease; a history of stroke, transient ischemic attack, or cerebral haemorrhage; peripheral arterial disease; atrial fibrillation and other arrhythmias; heart-valve disease; chronic obstructive pulmonary disease; chronic kidney disease; chronic liver disease; carotid-artery stenosis or occlusion; venous thromboembolic events; and heart failure. [h] Search criteria included “myocardial infarction” (broad standardized Medical Dictionary for Regulatory Activities [MedDRA] query) and “central nervous system haemorrhages and cerebrovascular conditions” (broad standardized MedDRA query).

B.2.3.2.2. Study C27003 baseline characteristics

A total of 103 patients were enrolled in this study. Sixty-three of the 65 patients (97%) randomised to relugolix and all 38 patients randomised to degarelix completed the 24wk treatment period and the 12-wk follow-up period. Two patients in the relugolix arm did not complete the study: one due to patient withdrawal and the other due to loss to follow-up. All patients were included in efficacy and safety analyses.

Patient demographics and baseline characteristics (Table 9) were similar between treatment groups. Most patients had intermediate-risk disease; however, two patients in each group with Gleason 9 disease and one patient in each group with T3 disease were allowed per protocol based on investigator discretion despite higher-risk disease. Overall, 18 patients had missing Gleason scores that the contract research monitoring team was unable to document at the enrolling sites. Median compliance with study drug, as measured with the electronic patient diary, was >98% in both arms.

Table 9: Patient demographics and baseline characteristics of Study C27003

(C27003) Baseline characteristic	Relugolix 120 mg QD	Degarelix 80 mg Q4W
	(n= 65)	(n=38)
Race, n (%) White Black or African American	 58 (89) 7 (11)	 31 (82) 7 (18)
Median (IQR) age (yr)	71.0 (67–73)	70.5 (67–75)
ECOG PS 0/1, [a]n (%)	60 (92)/4 (6)	33 (87)/4 (11)
Median (IQR) time since initial diagnosis (yr)	0.2 (0.1–0.3)	0.1 (0.1–0.2)
Gleason score,[b]n (%) 6 7 8 9	 5 (8) 40 (62) 5 (8) 2 (3)	 2 (5) 26 (68) 3 (8) 2 (5)
Primary tumour (T), n (%) Not available T1 T2 T2a T2b T2c T3 TX	 11 (17) 21 (32) 6 (9) 12 (18 7 (11) 7 (11) 1 (2) 0	 8 (21) 12 (32) 5 (13) 3 (8) 1 (3) 7 (18) 1 (3) 1 (3)
Regional lymph nodes (N), n (%) N0 NX[c]	 39 (60) 26 (40)	 19 (50) 19 (50)
PSA (µg/l) Mean (SD) Median (IQR)	 9.4 (6.0) 7.3 (4.8–12.9)	 14.6 (21.0) 7.3 (5.5–11.2)

ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; PSA = prostate-specific antigen; QD = once daily; Q4W = once every 4 wk; SD = standard deviation. [a]ECOG PS was missing for one patient in each group. [b]Total Gleason score was missing for 13 and five patients in the relugolix and degarelix groups, respectively. [c]NX includes unknown, not available, and missing regional lymph node data.

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical analysis for HERO and C27003 is available in Table 10. An overview of the key aspects for each trial then follows.

Table 10: Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT03085095 (HERO)	Hypothesis 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%. Hypothesis 2: relugolix is noninferior to leuprolide 3-month depot injection, as assessed by the cumulative probability of sustained testosterone suppression with a noninferiority margin of –10%.	mITT population, two-sided α = 0.05 significance level. If primary endpoint analysis met, key secondary endpoints were tested with a fixed-sequence testing procedure to maintain the overall familywise error rate of 0.05 for the testing of primary and key secondary endpoints	Sample size 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 and a dropout rate of 15%. For Hypothesis 1, 610 patients in the relugolix group would provide ~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 Hypothesis 2, with a noninferiority margin of -10% and an overall two-sided type I error rate of 0.05, a total of ~ 915 patients will yield at least 99% power to declare noninferiority of relugolix to	**By-visit endpoints** were analysed using observed data, unless otherwise specified. For observed data analyses, missing data was not imputed and only observed records were included. Patients who missed two or more consecutive visits after week 5 day 1 or discontinued from the study early were considered to have an event at the target day of the earliest missed visit. **Adverse Events**: The imputed dates were used to determine the treatment-emergent period. For AE with a partial date, available date parts of the partial date were compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. When in

			leuprolide. Actual sample: n=930 mITT population	doubt, the AE will be considered treatment emergent by default. **Concomitant medications:** When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). A per protocol analysis was carried out, as well as a sensitivity analysis to account for missing data or protocol deviations.
NCT02135445. (C27003)	The objective was to evaluate whether relugolix results in rapid and sustained testosterone suppression in men with intermediate-risk prostate cancer who require 6 months of neoadjuvant/adjuvant ADT in conjunction with EBRT. .	A one-sided 90% CI was used for the primary endpoint (rate of effective castration), and a two-sided 90% CI for the secondary endpoint of profound castration. No formal statistical differences were sought or hypothesised between relugolix and degarelix.	Assuming a 95% effective castration rate with relugolix treatment, 60 evaluable patients provided >91% as the lower bound of a one-sided 90% confidence interval. The sample size for the degarelix arm was based on historical estimates of castration rate using 80 mg 4-week depot dosing of > 95%, and no more	Patients were evaluated on days 1, 2, and 4 during week 1; once in each of weeks 2, 3, and 5; every 4 wk thereafter during the 24-wk treatment period; and for 12 wk after treatment discontinuation. QoL assessments were completed at screening; at baseline; after 4, 12, and 24 wk of treatment; 4 wk after treatment discontinuation; and at the end-of-study visit (36 wk after starting

		Changes in PSA, prostate volume, and testosterone levels were summarised over time. Changes in QoL values over time were analysed using linear mixed models. Time to castration and time to testosterone recovery were analysed using the Kaplan–Meier method. The safety population, defined as all patients who received one or more doses of either study drug, was used for all safety and efficacy analyses.	than two patients were expected to fail the defined successful castration endpoint. A total of 100 patients were planned to be enrolled into the study.	the study; 12 wk off treatment). Treatment compliance was measured by a patient-reported daily diary using a handheld electronic device. A per protocol analysis was carried out and censoring rules for Kaplan-Meier analysis are listed in section B.2.4.1.5. Sensitivity analysis was carried out on patients who missed two or more visits after week 5 Day 1 or discontinued from the study.

B.2.4.1. HERO study

B.2.4.1.1. Hypotheses

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

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

  Null hypothesis H_{01}: $\pi R < 0.9$ versus Alternative hypothesis Ha1: $\pi R \geq 0.9$

- Hypothesis 2, corresponding to Evaluation Criterion 2: relugolix is noninferior to leuprolide 3-month depot injection, as assessed by the cumulative probability of sustained testosterone suppression with a noninferiority margin of –10%.

  Null hypothesis H_{02}: $\pi R - \pi L < -10\%$ versus Alternative hypothesis Ha2: $\pi R - \pi L \geq -10\%$

where πR and πL are the sustained castration rates for the relugolix and leuprolide groups, respectively.

B.2.4.1.2. Sample size

Sample size 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. The 10% noninferiority margin for the comparison of relugolix versus leuprolide as well as studies of branded GnRH receptor agonist generics.

The primary analysis was performed separately for each evaluation criterion using data collected through 48 weeks after enrolment of approximately 915 patients.

B.2.4.1.3. Statistical Analyses

If the result of the primary endpoint was statistically significant, the alpha-protected key secondary endpoints were analysed. For Evaluation Criterion 2, the noninferiority margin was −10 percentage points. If noninferiority was demonstrated, testing for statistical superiority was performed using the same 95% CI without multiplicity adjustments (58).

The primary and 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 was <0.05. If the result of the primary endpoint analysis met the respective evaluation criterion, the key secondary endpoints were then tested with a fixed-sequence testing procedure to maintain the overall familywise error rate of 0.05 for the testing of primary and key secondary endpoints (58),

The sustained castration rate was estimated for each treatment group using the Kaplan-Meier method. To determine whether the sustained castration rate (defined as the cumulative probability of testosterone suppression to <50 ng/dL [1.7 nmol/L] while on study treatment from Week 5 Day 1 through Week 49 Day 1) for relugolix was ≥90%, the lower bound of the 95% CI for the cumulative probability of sustained testosterone suppression in the relugolix treatment group was calculated (58). Patients who did not have testosterone levels of <50 ng/dL at Day 29 or who had a testosterone level ≥50 ng/dL at any subsequent visit were determined to have an event of ineffective castration. Data for patients who discontinued treatment before a testosterone level ≥50 ng/dL was observed were censored at the last testosterone assessment before discontinuation (58).

B.2.4.1.4. Analysis populations

To assess different endpoints, the HERO study included a predefined primary analysis of safety and efficacy. The primary analysis of safety and efficacy occurred after 934 patients were randomized to the study and completed the 48-week treatment period and 30-day safety follow-up visit or discontinued early.

B.2.4.1.4.a. Modified Intention-to-Treat Population

The 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. The mITT population was the primary population used for efficacy endpoint analysis.

B.2.4.1.4.b. Per-Protocol Population

The per-protocol population was defined as those members of the mITT population who did not have important protocol deviations. This population was used for sensitivity analysis of the mITT population for the primary efficacy endpoint.

B.2.4.1.4.c. Safety Population

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.

B.2.4.1.5. Efficacy Analysis

The following subsections report on the primary efficacy endpoints and key secondary endpoints of the HERO study for the main (primary) analysis. 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 was less than 0.05. If the result of the primary endpoint was statistically significant, the alpha-protected key secondary endpoints were to be further tested.

B.2.4.1.5.a. Primary Efficacy Endpoints

The EMA appropriate primary efficacy endpoint for HERO was to establish the noninferiority of relugolix compared with leuprolide 3-month depot injection, as assessed by the cumulative probability of sustained testosterone suppression and was the first to be tested in the order of ranked endpoints (Table 11) to assess noninferiority of relugolix compared with leuprolide.

Evaluation Criterion 1 was a regulatory requirement from the FDA and was the trial success criterion for the main (primary) analysis. The FDA-appropriate primary

endpoint was the sustained castration rate (defined as the cumulative probability of testosterone suppression to <50 ng/dL) of relugolix through 48 weeks of treatment.

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

Definition of testosterone test result at Week 5 Day 1

Serum concentrations of testosterone at Week 5 Day 1 were obtained at Day 29, with a visit window from Day 22 to Day 43, inclusive. If more than one test result was available within the visit window, the result with the study day closest to Day 29 target date was used. If there were two results equidistant to the scheduled target study day, the earlier assessment was used as testosterone test result for Week 5 Day 1.

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.

B.2.4.1.5.b. Key secondary endpoints

Key secondary endpoints were tested in the order shown in Table 11 for different regulatory agencies, with a fixed-sequence testing procedure to control the overall familywise error rate at a two-sided type I error rate of 0.05 across primary and key secondary endpoints. Definitions and data presentations for the key secondary efficacy endpoints analysed in the study for the primary analysis are as follows:

- Castration rate, defined as the cumulative probability of testosterone suppression to < 50 ng/dL using the Kaplan-Meier method:

    - prior to dosing at Week 1 Day 4, and
    - prior to dosing at Week 3 Day 1
- Profound castration rate, defined as the cumulative probability of testosterone suppression to < 20 ng/dL prior to dosing at Week 3 Day 1; summarized by treatment group using the Kaplan-Meier method;
- PSA response rate, 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) (Scher et al. 2016); summarized and compared between the relugolix group and the leuprolide group;
- FSH concentrations and percent change from baseline in FSH at Week 25 Day 1, summarized and compared between the relugolix group and the leuprolide group;
- CRFS was defined by disease progression despite achieving testosterone suppression to castrate levels (< 50 ng/dL)

Cumulative probability of testosterone recovery (back to > 280 ng/dL) at the 90-day follow-up visit was to be evaluated in approximately 100 patients randomized to relugolix and approximately 50 patients randomized to leuprolide who complete 48 weeks of treatment and who do not start alternative ADT within the following 12 weeks (or within 24 weeks following the last received leuprolide 3-month depot injection). Results were to be compared between the relugolix group and the leuprolide group and reported in the final analysis; however, at the primary analysis, this endpoint was analysed for exploratory purposes without formal testing.

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Table 11: Testing order and timing of analysis for primary and key secondary endpoints for different regulatory agencies

	Testing order for the FDA		Testing order for the EMA	
Endpoints	At primary analysis	At final analysis	At primary analysis	At final analysis
Sustained castration rate per Evaluation Criterion 1 (≥ 90% in relugolix)	1	Update	NA	Update
Sustained castration rate per Evaluation Criterion 2 (noninferiority of relugolix compared with leuprolide acetate)	2	Update	1	Update
Castration rate on Week 1 Day 4	3	Update	2	Update
Castration rate on Week 3 Day 1	4	Update	3	Update
Confirmed PSA response rate at Week 3 Day 1	5	Update	4	Update
Profound castration rate at Week 3 Day 1	6	Update	5	Update
FSH level at Week 25 Day 1	7	Update	6	Update
CRFS during the 48-week treatment in patients with metastatic prostate cancer [a]	NA	8	NA	7
CRFS 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 a	10 [b]	NA	9 [b]	NA

Abbreviations: FDA = Food and Drug Administration; FSA = follicle-stimulating hormone; NA = not applicable; PSA = prostate-specific antigen. [a] CRFS (castration-resistant free survival) and time to testosterone recovery back to 280 ng/dL at the 90-day follow-up will be tested at the final analysis only if all the above endpoints reach statistical significance in the primary analysis. Endpoints in the higher order will be updated with descriptive statistics in the final analysis. [b] Analysis of time to testosterone recovery back to 280 ng/dL at the 90-day follow-up was performed at the primary analysis exploratory purposes without formal testing. Testing order of time to testosterone recovery will be preceded by castration resistance-free survival in the final analysis.

B.2.4.1.5.c. 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.

B.2.4.1.5.d. Exploratory efficacy endpoints

Overall survival was defined as time from randomization to date of death prior to data cut-off date. 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 data cut-off date.

B.2.4.1.5.e. Patient-reported outcomes

Patient reported outcome 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.

Missing Items: For multi-item scales, if at least half of the items from the scale had been answered, the raw score calculation was applied to the items that were completed. Otherwise, the scale score was set to missing. For single-item scales, the score was set to missing if the response of the item was missing.

B.2.4.1.6. Safety analyses

Safety was assessed throughout the study by monitoring adverse events (59). The severity of all treatment-emergent adverse events was evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and was coded to preferred term, higher level term, and system organ class using MedDRA. Adverse event categories for safety parameters of interest for relugolix were:

- Loss of bone mineral density

- QTc prolongation
- Hepatic transaminase elevations
- Carbohydrate and lipid metabolic effects
- Adverse cardiovascular events (which includes MACE)
- Vasomotor symptoms
- Mood disorders
- Hypersensitivity

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. 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).

B.2.4.2. Study C27003

B.2.4.2.1. Sample size

Assuming a 95% effective castration rate (<1.73 nmol/l or 50 ng/dl) with relugolix treatment, 60 evaluable patients provided >91% as the lower bound of a one-sided 90% confidence interval (CI). The sample size for the degarelix arm was based on historical estimates of castration rate using 80-mg 4-wk depot dosing of >95% (60), and no more than two patients were expected to fail the defined successful castration endpoint. A total of 100 patients were planned to be enrolled into the study. In addition to the one-sided 90% CI for the primary endpoint, two-sided 95% CIs were calculated for the primary endpoint and the secondary endpoint of profound castration. No formal statistical differences were sought or hypothesised between relugolix and degarelix.

B.2.4.2.2. Statistical Analysis

The primary endpoints from the supportive phase 2 study (C27003) were analysed using descriptive statistics by treatment group. There were no alpha-protected secondary endpoints and no treatment comparisons predefined for these studies.

Changes in PSA, prostate volume, and testosterone levels were summarised over time. Changes in QoL values over time were analysed using linear mixed models. Time to castration and time to testosterone recovery were analysed using the Kaplan–Meier method. The safety population, defined as all patients who received one or more doses of either study drug, was used for all safety and efficacy analyses.

B.2.4.2.3. Analysis populations

The efficacy and safety analyses were conducted in all randomly assigned patients who took at least one dose of trial treatment (53).

B.2.4.2.4. Efficacy analysis

The primary efficacy endpoint was the rate of effective castration between 4 and 24 weeks of treatment, defined as the estimated proportion of patients with testosterone concentrations <50 ng/dL at all scheduled visits. Secondary endpoints were:

- Time to achieve effective castration (<50 ng/dL)
- Time to achieve profound castration (20 ng/dL)
- Time to testosterone recovery (defined as the return of testosterone values to baseline or to >280 ng/dL)
- Prostate volume 8 to 12 weeks after treatment
- PSA response at 12 weeks.

B.2.4.2.5. Safety Analysis

Safety assessments included incidence and severity of treatment-emergent adverse events, changes in vital signs, laboratory studies and ECGs.

B.2.4.2.6. *Other Analysis*

Patient-reported outcome questionnaires (EORTC-QLQ-C30, EORTC-QLQ-PR25, and Aging Males' Symptoms scale) 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 at the 60- and 90-day testosterone recovery follow-up visits if patients were participating in the testosterone recovery follow-up.

B.2.5. Critical appraisal of the clinical effectiveness evidence for relugolix

The HERO trial and Study C27003 were assessed for quality using the York Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare. The summary of the findings is presented in Table 12.

Table 12: Summary of the quality assessment results

Trial number (acronym)	HERO	C27003
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	This was an open label study. However, outcome assessors were blind to treatment allocation	No. [This study was not sponsored by Accord therefore detailed information on blinding was not available].
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

The HERO trial was a robust randomised controlled trial (RCT) that included randomisation without any imbalances in the dropouts between groups and no evidence to suggest any measurement of more outcomes than reported.

The C27003 trial was a robust RCT that included randomisation without any imbalances in the dropouts between groups and no evidence to suggest any measurement of more outcomes than reported.

The complete quality assessment for each study is presented in Appendix D: Identification, selection and synthesis of clinical evidence.

B.2.5.1. Measures to minimize bias

B.2.5.1.1. HERO trial

After a patient was screened and the investigator determined that the patient was eligible for enrolment, the site staff completed the Randomization Authorization Form capturing key eligibility criteria and concomitant medications and sent it to the sponsor per the instructions in the investigator site file. The sponsor, including the

medical monitor and an assigned member of the clinical operations team, reviewed the Randomization Authorization Form and the patient's de-identified screening laboratory evaluations, and if approved, the patient's Randomization Authorization Form was signed and approved in writing. Once the site received approval, the patient could undergo the baseline Day 1 visit, during which the site randomized the patient to treatment by using the IWRS. The IWRS assigned the patient identification (ID) number which identified the patient for the duration of the study. A study drug kit number available at the site was assigned to the patient by the IWRS according to the randomization code. Randomization was stratified by geographic region, presence of metastatic disease and age.

B.2.5.1.2. Study C27003

Patients were randomised sequentially by study centre. No stratification was implemented in the computer-generated randomisation schedule. Unique randomisation numbers were assigned to patients using a centralised interactive voice/web response system.

B.2.5.2. Blinding

B.2.5.2.1. HERO trial

Blinding was not applicable; this was a randomized open-label study. Sponsor and vendor operational staff responsible for monitoring the quality of the data collected at the investigator sites had access to patient treatment data. Sponsor and vendor operational staff responsible for management of drug supply for the study had access to the randomization system, but not the clinical data collected at the investigator sites. The study statistician remained blinded until the SAP for the primary analysis of the study was finalized. Access to the testosterone results through the liquid chromatography with tandem mass spectrometry method done at the bioanalytical laboratory was very limited as was access to any unblinded aggregated data. A single representative from clinical operations and data management and the medical monitor were provided the bio-analytical results.

The primary and secondary endpoints were based upon testosterone, PSA and FSH results assessed and reported by a central laboratory. These data allowed for

evaluation of study success using objective measures not influenced by the open-label nature of the study.

B.2.5.2.2. Study C27003

Blinding was not applicable as this was a randomized, open-label study.

B.2.5.3. Generalisability of the evidence to routine clinical practice in England

B.2.5.3.1. HERO trial

The trial included men with all stages of advanced prostate cancer in which ADT is currently indicated and only 9.8% of patients had non- classifiable prostate cancer. Of note, only 23.4% of patients had protection against flare whereas in clinical practice, people having hormonal therapy with GnRH agonists also have 28 days treatment with an anti-androgen, such as bicalutamide for protection against testosterone flare. ADT is often used in combination with agents, such as enzalutamide or docetaxel. In HERO, only a small subset of patients received either enzalutamide (n = 17; 2.7%) or docetaxel (n < 10; <1.3%).

Relugolix was administered as 120 mg orally once daily. The dose of leuprolide was 22.5 mg (or 11.25 mg in Japan and Taiwan based on local labels), administered every 3 months by subcutaneous injection. Although the BNF suggests a dose of 11.25 mg every 3 months by subcutaneous injection (61), the dose of leuprolide 3-month depot injection was selected as per product instructions provided by the manufacturer (Eligard Prescribing Information 2019) (62) and the 11.25mg dose (Prostap 3 DCS 11.25mg SmPC 2019) (63). It is assumed that if anything, a higher dose would result in a bigger clinical benefit (personal communication, 2023).

B.2.5.3.2. Study C27003

The C27003 trial included men with intermediate-risk prostate cancer in which ADT was indicated, in combination with EBRT. The study also included a small proportion (3 patients) in each group with high-risk disease. Overall, 18 patients had missing Gleason scores that the contract research monitoring team was unable to document at the enrolling sites.

B.2.6. Clinical effectiveness results of the relevant studies

B.2.6.1. HERO study clinical effectiveness

Efficacy and safety data from participants in the relugolix and leuprolide groups of the Phase 3 HERO study are presented and utilized in the model and relate to the submission population and drug indication.

B.2.6.1.1. Primary efficacy endpoint

The study had two separate evaluation criteria for the primary efficacy endpoint to support different regulatory requirements for assessing efficacy (described in B.2.4.1.5).

B.2.6.1.2. Primary analysis

The study met its primary endpoint based on both evaluation criteria. A total of 96.7% of patients who received relugolix achieved and maintained sustained testosterone suppression below castrate levels (< 50 ng/dL) from Week 5 Day 1 (Day 29) to Week 49 Day 1 (Day 337) (95% CI: 94.9%, 97.9%) with the lower bound of the 95% CI exceeding 90%. In comparison, a total of 88.8% patients who received leuprolide achieved and maintained sustained testosterone suppression below castrate levels from Week 5 Day 1 (Day 29) to Week 49 Day 1 (Day 337) (95% CI: 84.6%, 91.8%). The between-group difference of 7.9% (95% CI: 4.1%, 11.8%) demonstrated not only noninferiority of relugolix to leuprolide (the lower bound of the 95% CI for the difference between groups was greater than the pre-specified noninferiority margin of −10%), but also statistical superiority of relugolix compared with leuprolide (lower bound of the 95% CI greater than 0, with $p < 0.0001$).

The hazard ratio comparing relugolix with leuprolide for risk of testosterone escape was 0.26 (95% CI: 0.15, 0.46, which excluded 1), indicating relugolix significantly reduced the risk of testosterone escape by 74% compared with leuprolide.

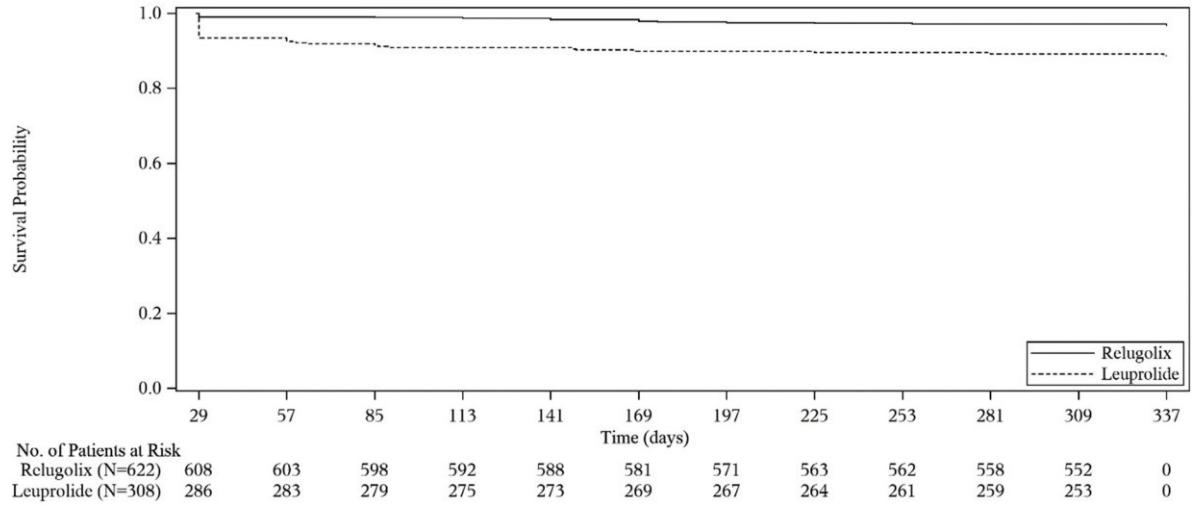
A summary of the primary endpoint analysis is presented in Table 13 and an overview of the Kaplan-Meier Analysis for sustained castration rate is presented by treatment group in Figure 4.

Table 13: Summary of the primary endpoint analysis (mITT population)

Primary Endpoint Sustained castration rate (< 50 ng/dL) from Day 29 through Day 337	**Relugolix** **(N=622)**	**Leuprolide** **(N=308)**
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] p-value [c]	7.9% (4.1%, 11.8%) <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 noninferiority margin for the difference from leuprolide was −10%.

Figure 4: Kaplan-Meier survival curve of sustained castration rate (< 50ng/dL) (mITT Population)



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

B.2.6.1.3. Sensitivity analysis

To assess the robustness of the primary analysis for Evaluation Criterion 1 and 2, sensitivity analysis of the primary endpoint was performed.

In the primary analysis, the estimated castration rate in the leuprolide group was more affected by events due to missing testosterone levels or testosterone levels exceeding 50 ng/dL at Week 5 Day 1 (Day 29) than in the relugolix group (6 patients [1.0%] in relugolix group vs 20 patients [6.5%] in leuprolide group) using the censoring rules as specified in the statistical analysis plan. Among the six relugolix patients who were defined as treatment failures, four had non-castrate levels of testosterone and two had missing assessments. Among the 20 leuprolide patients who were defined as treatment failures, 17 had non-castrate levels of testosterone and three had missing assessments.

To assess the impact of delayed testosterone suppression to castrate levels seen in the primary analysis, analysis of the primary endpoint (Sensitivity Analysis 4) was repeated with the consideration that patients who had assessments and did not reach castrate levels of testosterone at Week 5 Day 1 were censored at Week 5 Day 1. A total of 4 pre-specified sensitivity analyses were conducted to test the robustness of the primary analyses (for both Criterion 1 and Criterion 2).

The results of these sensitivity analyses of the primary endpoint are provided in Table 14.

Table 14: Sensitivity analysis of Kaplan-Meier estimates for sustained castration rate from Day 29 to Day 337

	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%				89.7%
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] Difference from leuprolide at Day 337 95% CI for difference from leuprolide at Day 337[e] p-value[f] Hazard ratio to leuprolide (95% CI)[g]				(85.8%, 90.9%) 5.0% (0.1%, 9.8%) 0.0368 0.6461 (0.4476, 0.9326)				(79.0%, 87.4%)
Sensitivity 4 mITT population Day 337 95% CI at Day 337[d] Difference from leuprolide at Day 337 95% CI for difference from leuprolide at Day 337[e] p-value[f] Hazard ratio to leuprolide (95% CI)[g]	622 0	15	607	97.3% (95.6%, 98.4%) 3.3% (0.2%, 6.4%) 0.0202 0.4124 (0.2058, 0.8263)	308 0	17	291	94.0% (90.5%, 96.2%)

The database lock date was 10 Dec 2019. 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 did not castrate 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. The noninferiority margin for the difference from leuprolide was -10%.

The results of Sensitivity Analysis 1 (a repeated analysis of the primary endpoint in the per-protocol population) and Sensitivity Analysis 2 (an analysis excluding patients who had received concomitant medications and herbal supplements that could possibly affect testosterone levels during study treatment) were also consistent with the results from the primary analysis of the primary endpoint. Both sensitivity analysis successfully met Evaluation Criterion 1 with the lower bound of the 95% CI (94.5%, 97.7%) exceeding 90% and demonstrated both noninferiority and superiority to leuprolide (Evaluation Criterion 2).

Sensitivity Analysis 3 was an analysis with patients who had missed two or more consecutive visits after Week 5 Day 1 or discontinued from the study early was considered as an event at the target day of the earliest missed visit. An estimated 88.6% (95% CI: 85.8%, 90.0%) of patients in the relugolix group achieved and maintained sustained testosterone suppression below castrate levels (< 50 ng/dL) for 48 weeks compared with 83.7% (95% CI: 79.0%, 87.4%) of patients in the leuprolide group. Although the lower bound of the 95% CI for the relugolix group was less than 90%, the between-group difference of 5.0% (95% CI: 0.1%, 9.8%) demonstrated not only noninferiority to leuprolide (the lower bound of the 95% CI for difference between groups was greater than a pre-specified noninferiority margin of −10%), but also statistical superiority to leuprolide (nominal p = 0.0368). The early discontinuation rate was approximately 10% in each group which explains the lower response rates in this analysis compared with the primary analysis. The 21 patients (17 in the leuprolide group and four in the relugolix group) who did not achieve castrate levels of testosterone at Week 5 Day 1 were discontinued from the study early and were thus deemed events in both this sensitivity analysis and the primary analysis. The higher proportion of these patients in the leuprolide group explains the slightly smaller lowering of the rate in that group compared with the relugolix group, though the magnitude of lowering is still very similar in both groups.

Sensitivity Analysis 4 was conducted to assess the impact of delayed testosterone suppression to castrate levels by Week 5 Day 1 (Day 29). In the primary analysis, the estimated castration rate in the leuprolide group was more affected by events due to missing testosterone levels or levels exceeding 50 ng/dL at Week 5 Day 1 (Day 29) than in the relugolix group (six patients [1.0%] in the relugolix group vs 20

patients [6.5%] in the leuprolide group). Analysis of the primary endpoint was repeated with the consideration that patients who had not reached castrate levels of testosterone at Week 5 Day 1 (Day 29) were censored at Week 5 Day 1 and not deemed to have had an event. This analysis censored the 21 patients who were non-castrate at Week 5 Day 1 (Day 29) (17 in leuprolide and four in relugolix) and left the remaining five patients (three in leuprolide and two in relugolix) with missing assessments at Week 5 Day 1 (Day 29) as having events. The results of Sensitivity Analysis 4 were consistent with the results from the primary analysis of the primary endpoint. An estimated 97.3% (95% CI: 95.6%, 98.4%) of patients in the relugolix group achieved and maintained sustained testosterone suppression below castrate levels (< 50 ng/dL) for 48 weeks compared with 94.0% (95% CI: 90.5%, 96.2%) of patients in the leuprolide group. Consistent with the primary analysis, the lower bound of the 95% CI for the relugolix group was above 90%, meeting Evaluation Criterion 1, and relugolix demonstrated not only noninferiority to leuprolide (lower bound of the 95% CI for difference between groups was greater than a pre-specified noninferiority margin of −10%), but also statistical superiority to leuprolide (lower bound of the 95% CI for the difference was greater than 0, with nominal p = 0.0202).

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. In Sensitivity Analysis 3, both groups were evenly affected by patients who discontinued early from the study, and despite the lower rates in both groups, the results were generally consistent with the primary analysis.

All four sensitivity analyses demonstrated not only noninferiority of relugolix compared with leuprolide, but also statistical superiority of relugolix compared with leuprolide.

B.2.6.1.4. Secondary Efficacy Endpoints

The secondary efficacy analyses for this study were divided into alpha-protected, key secondary endpoints, other secondary endpoints and exploratory endpoints.

B.2.6.1.5. Overview of alpha-protected key secondary endpoints

Before the key secondary endpoints were tested, Evaluation Criterion 1 followed by Evaluation Criterion 2 for health authorities aside from the FDA must first have been met (see section B.2.4.1.3). As the results of both Evaluation Criterion 1 and Evaluation Criterion 2 of the primary endpoint were statistically significant, the alpha-protected key secondary endpoints were tested in hierarchical order. Results of the alpha-protected secondary efficacy endpoints are provided in Table 15.

Table 15: Alpha-protected secondary efficacy endpoints

Endpoint	Relugolix (N = 622)	Leuprolide (N = 308)	P-value
Cumulative probability of testosterone suppression to < 50 ng/dL prior to dosing on Week 1 Day 4	56.04	0.00	<0.0001
Cumulative probability of testosterone suppression to < 50 ng/dL prior to dosing on Week 3 Day 1	98.71	12.05	<0.0001
Proportion of patients with PSA response at Week 3 Day 1followed with confirmation at Week 5 Day 1	79.4	19.8	<0.0001
Cumulative probability of testosterone suppression to < 20 ng/dL prior to dosing on Week 3 Day 1	78.38	0.98	<0.0001
Mean FSH (IU/L) at Week 25 Day 1	1.72	5.95	<0.0001

The database lock date was 10 Dec 2019. Abbreviations: FSH = follicle-stimulating hormone; PSA = prostate-specific antigen

All alpha-protected key secondary endpoints tested demonstrated superiority of relugolix over leuprolide ($p < 0.0001$). Details for each endpoint are provided in the subsequent sections.

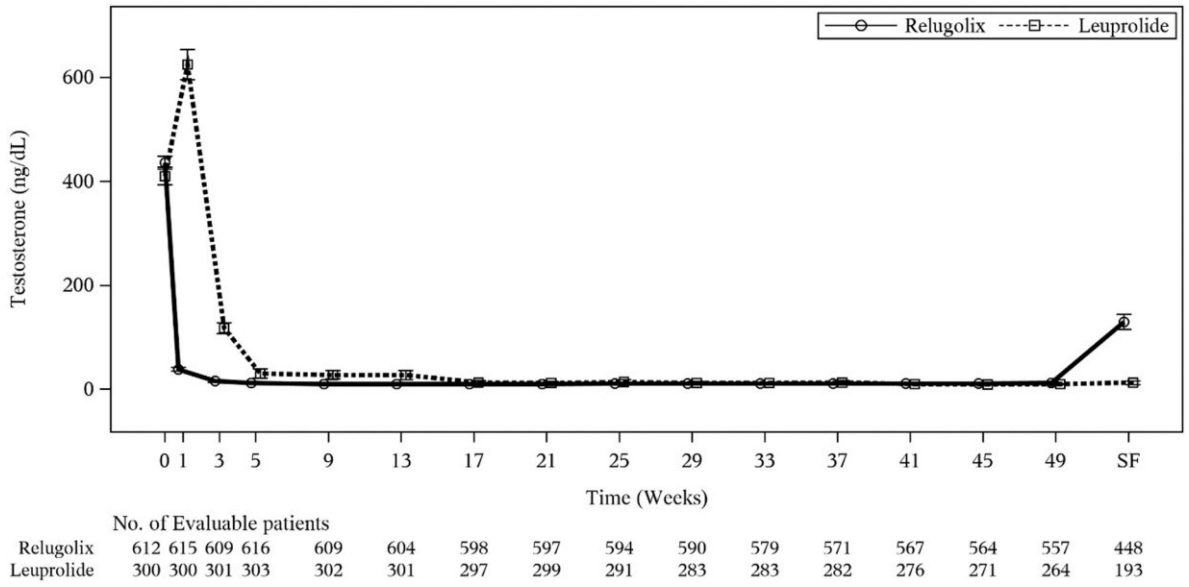
B.2.6.1.6. Testosterone-related secondary endpoints

Testosterone-related secondary endpoints included alpha-protected key secondary endpoints (castration rate at Week 1 Day 4 [Day 4] and Week 3 Day 1 [Day 15] and profound castration rate at Week 3 Day 1 [Day 15]) and other secondary endpoints including assessments of rapid castration, profound castration, and time to testosterone recovery.

B.2.6.1.6.a. Testosterone levels over time during treatment

Testosterone concentrations over time are presented in Figure 5

Figure 5: Testosterone concentrations over time (mITT population)



The database lock date was 10 Dec 2019. Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SF = Safety follow up. Mean (95% CI) are presented.

By Week 1 Day 4 (Day 4) of treatment with relugolix, mean testosterone levels were below the 50 ng/dL threshold demonstrating rapid onset of testosterone suppression with no initial increase in testosterone. In contrast, a surge in testosterone levels from baseline to Week 1 Day 4 (Day 4) was observed in the leuprolide group, consistent with the initial direct agonist mechanism of action of GnRH receptor agonists, before decreasing to castrate levels at Week 5 Day 1 (Day 29). Thereafter, testosterone levels remained suppressed from Week 5 Day 1 (Day 29) to Week 49 Day 1 (Day 337). Testosterone levels began to recover above castrate levels 30 days after the discontinuation of relugolix while patients in the leuprolide group remained castrated.

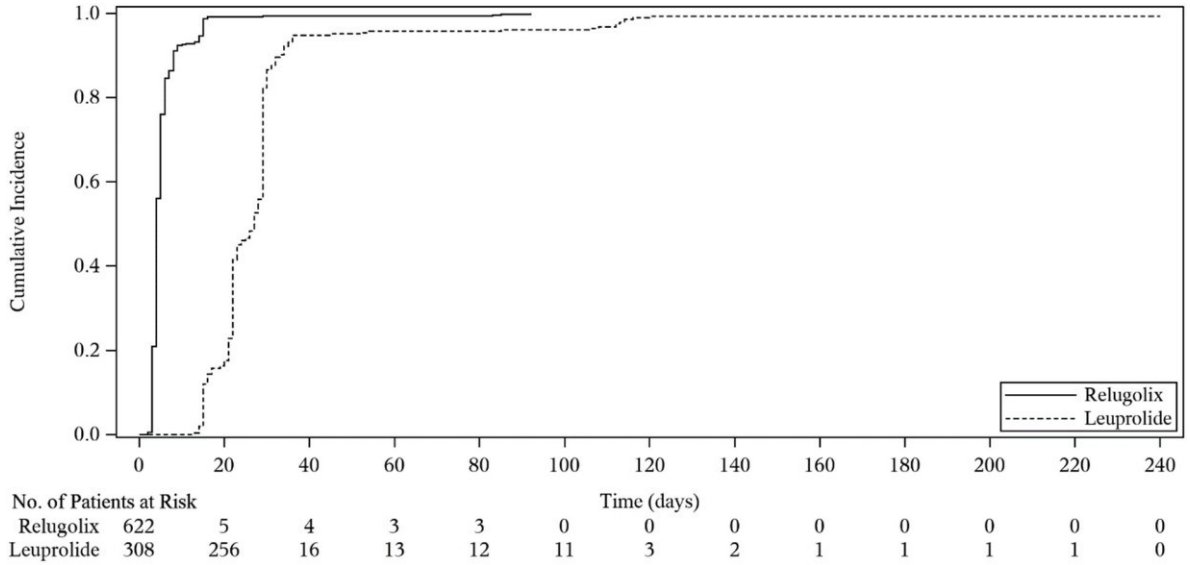
Change in testosterone concentration in the first 4 weeks of treatment are presented in Appendix M: Additional clinical evidence (M1.1).

B.2.6.1.6.b. Time to initial castration (testosterone < 50 ng/dL)

Castration rates, defined as the cumulative probability of testosterone suppression to < 50 ng/dL at Week 1 Day 4 (Day 4) and Week 3 Day 1 (Day 15), were alpha-protected key secondary endpoints and were estimated via the Kaplan-Meier method based on time to first testosterone castration. The cumulative incidence of time to

initial castration (testosterone < 50 ng/dL) is presented in Figure 6 and Kaplan-Meier estimates are provided in Appendix M: Additional clinical evidence (Table 117).

Figure 6: Cumulative incidence of time to initial castration (testosterone < 50 ng/dL) (mITT population)



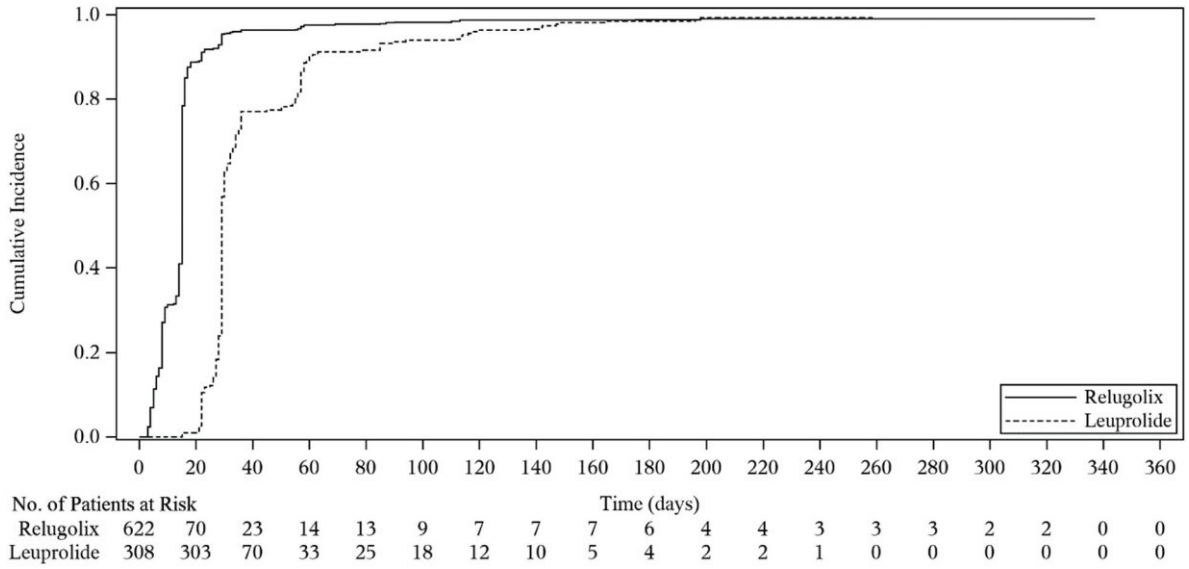
The database lock date was 10 Dec 2019. Abbreviation: mITT = modified intent-to-treat.

Time to initial castration was faster for the relugolix group compared with the leuprolide group (Figure 6). By Week 1 Day 4 (Day 4), the castration rate was 56.04% in the relugolix group, compared with 0% in the leuprolide group ($p < 0.0001$) (Table 117). At Week 3 Day 1 (Day 15), the castration rate was 98.71% in the relugolix group and 12.05% in the leuprolide group, with a statistically significant difference of 86.66% ($p < 0.0001$). The median time to initial castration was 4 days in the relugolix group compared with 27 days in the leuprolide group, further supporting the ability of relugolix to rapidly achieve testosterone suppression.

B.2.6.1.6.c. Time to profound castration (testosterone < 20 ng/dL)

Profound castration rates, defined as the cumulative probability of testosterone suppression to < 20 ng/dL Week 3 Day 1 (Day 15) was an alpha-protected key secondary endpoint. The cumulative incidence of time to profound castration (testosterone < 20 ng/dL) is presented in **Figure** 7 and Kaplan-Meier estimates are provided in Appendix M: Additional clinical evidence (Table 118).

Figure 7: Cumulative incidence of time to initial profound castration (testosterone < 20 ng/dL) (mITT population)



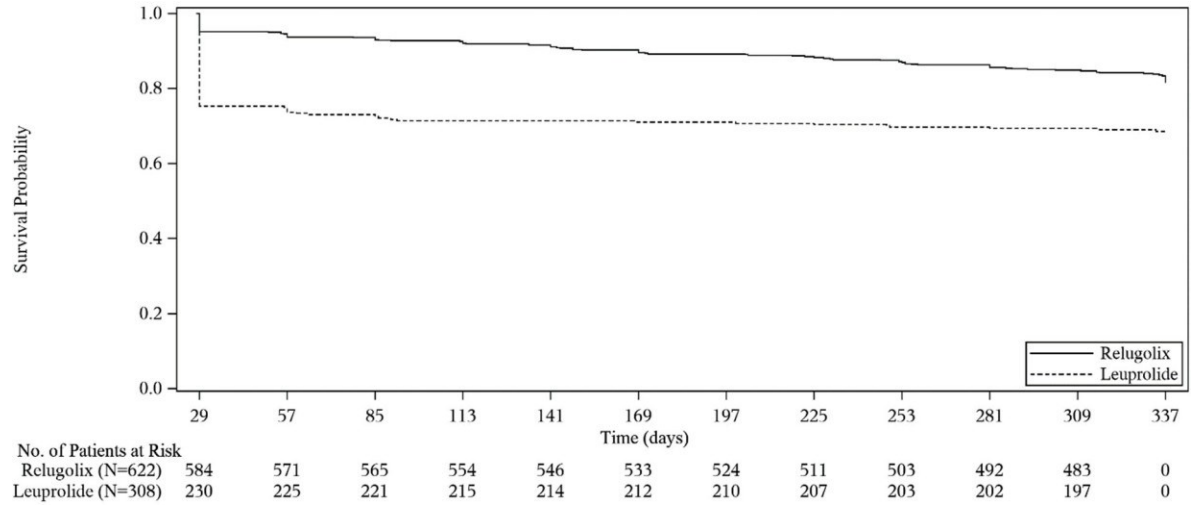
The database lock date was 10 Dec 2019. Abbreviation: mITT = modified intent-to-treat.

Time to profound castration was faster for the relugolix group compared with the leuprolide group (**Figure** 7). By Week 1 Day 4 (Day 4), the profound castration rate was 6.92% in patients receiving relugolix and 0% in patients receiving leuprolide (Table 118). At Week 3 Day 1 (Day 15), the profound castration rate was even greater in the relugolix group (78.38%) compared with patients in the leuprolide group (0.98%), with a statistical difference of 77.41% ($p < 0.0001$). The median time to profound castration was also shorter in the relugolix group (15.0 days) compared with the leuprolide group (29.0 days).

B.2.6.1.6.d. Sustained profound castration rate

Sustained profound castration rate, defined as the cumulative probability of testosterone suppression to < 20 ng/dL, was estimated via the Kaplan-Meier method from Week 5 Day 1 (Day 29) through Week 49 Day 1 (Day 337). An overview of the Kaplan-Meier Analysis for sustained profound castration rate is presented by treatment group in Figure 8 and the cumulative probability analyses are presented in Appendix M: Additional clinical evidence (Table 119).

Figure 8: Kaplan-Meier Survival Curve of Sustained Profound Castration Rate (< 20 ng/dL) from Day 29 to Day 337 (mITT Population)



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

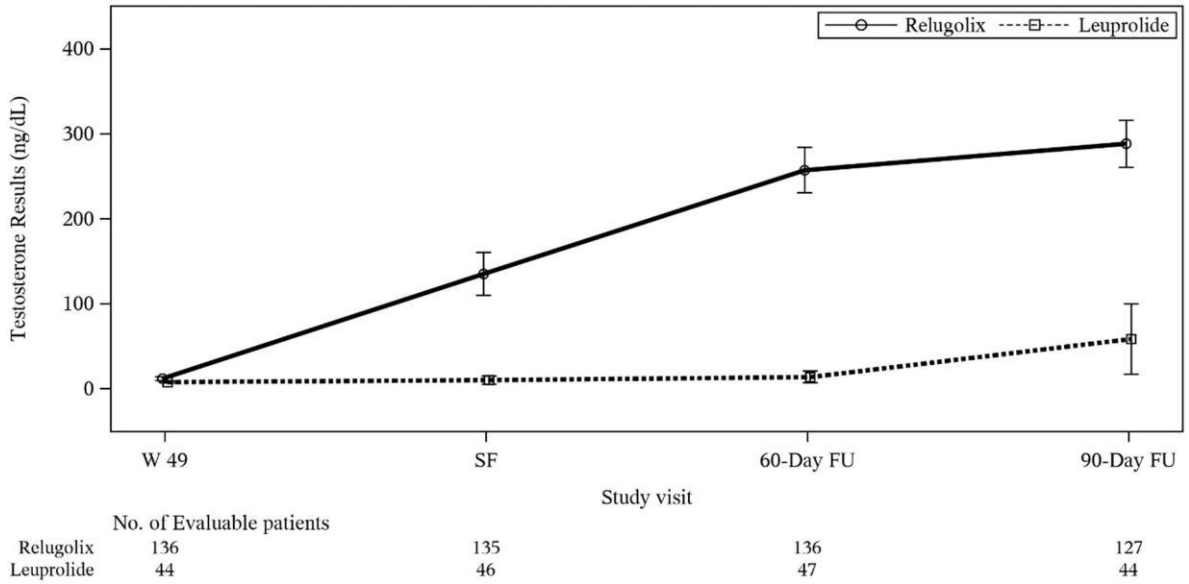
Sustained profound castration was higher for the relugolix group compared with the leuprolide group (Figure 8). At Week 49 Day 1 (Day 337), the profound castration rate was higher in patients receiving relugolix (81.6%; 95% CI: 78.1%, 84.5%) than in patients receiving leuprolide (68.6%; 95% CI: 63.0%, 73.5%), with a difference of 13.0% (Table 119). Relugolix was able to achieve and sustain profound testosterone suppression more rapidly compared with leuprolide. Testosterone levels remained below the profound castrate levels from Week 25 Day 1 (Day 169) through Week 49 Day 1 (Day 337) with relugolix and leuprolide.

B.2.6.1.6.e. Testosterone recovery after discontinuation of treatment

The assessment of testosterone recovery after discontinuation of relugolix and leuprolide included percentage change from baseline in testosterone during the recovery phase, summary of testosterone concentrations in the recovery phase, and time to testosterone recovery.

A total of 137 patients randomized to relugolix and 47 patients randomized to leuprolide completed 48 weeks of treatment and were followed for testosterone recovery at the 30-, 60-, and 90-day follow-up visits. Testosterone concentrations during the follow-up period are presented in Figure 9.

Figure 9: Testosterone concentrations in testosterone recovery phase (mITT population)



The database lock date was 10 Dec 2019. Abbreviations: CI = confidence interval; FU = follow-up; mITT = modified intent-to-treat; SF = safety follow-up. Mean (95% CI) are presented.

Testosterone recovery was observed after discontinuation of study drug. Patients in the relugolix group began to recover 30 days after study drug discontinuation, compared with patients in the leuprolide group who remained castrated. Testosterone levels in the leuprolide group remained below baseline levels through the 90-day follow-up visits following the last injection. The median testosterone values at baseline were similar for the relugolix group (409.62 ng/dL) and leuprolide group (399.12 ng/dL). At the 30-day follow up visit, patients who received relugolix had a median testosterone value of 77.47 ng/dL compared with 7.11 ng/dL in the leuprolide group. By the 90-day follow up visit, patients who received relugolix had a median testosterone value of 270.76 ng/dL compared with 12.26 ng/dL in the leuprolide group.

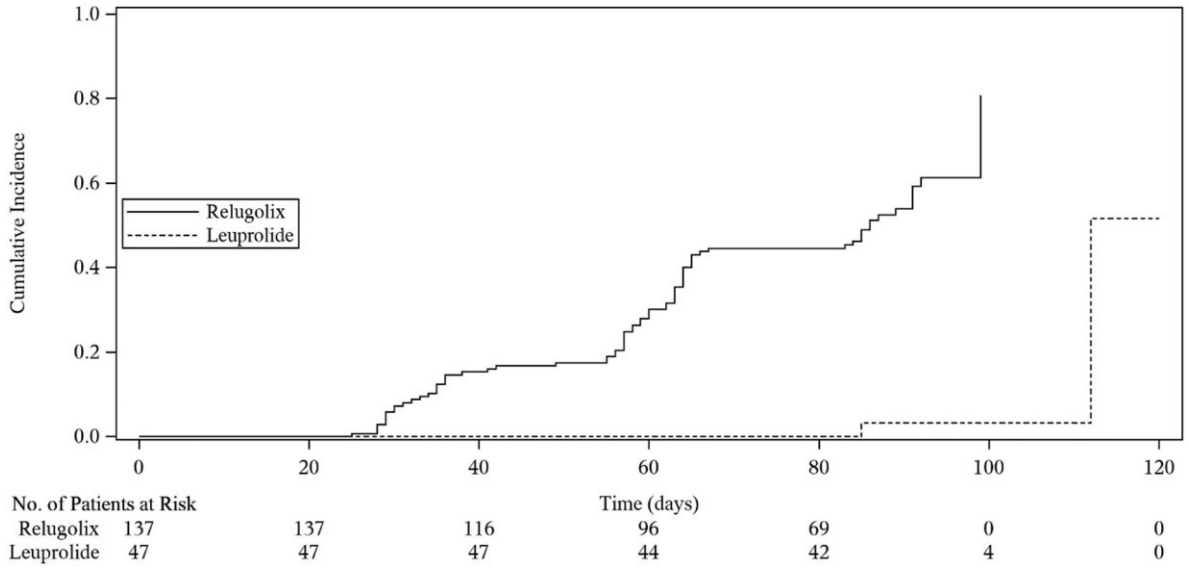
Details of testosterone recovery to categorical levels is presented in Appendix M: Additional clinical evidence (**Testosterone recovery to categorical levels**).

B.2.6.1.6.f. Time to testosterone recovery

Time to testosterone recovery at the 30-day, 60-day, and 90-day follow-up visits was summarised using the Kaplan-Meier method. Time to testosterone recovery back to > 280 ng/dL (lower limit of the normal range) at the 90-day follow-up visit was an

alpha-protected key secondary endpoint for the final analysis; however, for the primary analysis, this endpoint was analysed for exploratory purposes without formal testing. The cumulative incidence of time to testosterone recovery is presented in Figure 10, and Kaplan-Meier estimates are provided in Appendix M: Additional clinical evidence (Table 121).

Figure 10: Cumulative Incidence of Time to Testosterone Recovery (> 280 ng/dL) (mITT Population)



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

Time to testosterone recovery was faster for the relugolix group compared with the leuprolide group (Figure 10). Unlike other ADTs, relugolix, an oral nonpeptide GnRH receptor antagonist, has the unique advantage of a fast testosterone recovery after the patient discontinues the drug. The cumulative incidence rate of testosterone recovery to > 280 ng/dL at 90 days after drug discontinuation was 53.93% in the relugolix group compared with 3.23% in the leuprolide group (nominal p = 0.0017) (Table 121).

The median time to testosterone recovery to > 280 ng/dL was 86.0 days (95% CI: 65.0, 92.0) in the relugolix group and 112.0 days (95% CI: 112.0, not estimable) in the leuprolide group. The estimated median for the leuprolide group must be interpreted with caution because only 2 of the 47 patients were able to achieve recovery and the median was met when the risk set of patients was extremely small at the end of the recovery period.

Other secondary endpoints included the cumulative probability of testosterone recovery back to ≥ 50 ng/dL or back to ≥ 280 ng/dL or baseline at the 90-day follow-up in a subset of patients. In general, the results for recovery back to ≥ 280 ng/dL or baseline were similar to testosterone recovery back to > 280 ng/dL at the 90-day follow-up visit. A total of 133 of 137 relugolix patients reached testosterone levels ≥ 50 ng/dL during the recovery period resulting in an estimated recovery rate at the 90-day follow-up visit of 93.01% compared with 10.12% in the leuprolide group.

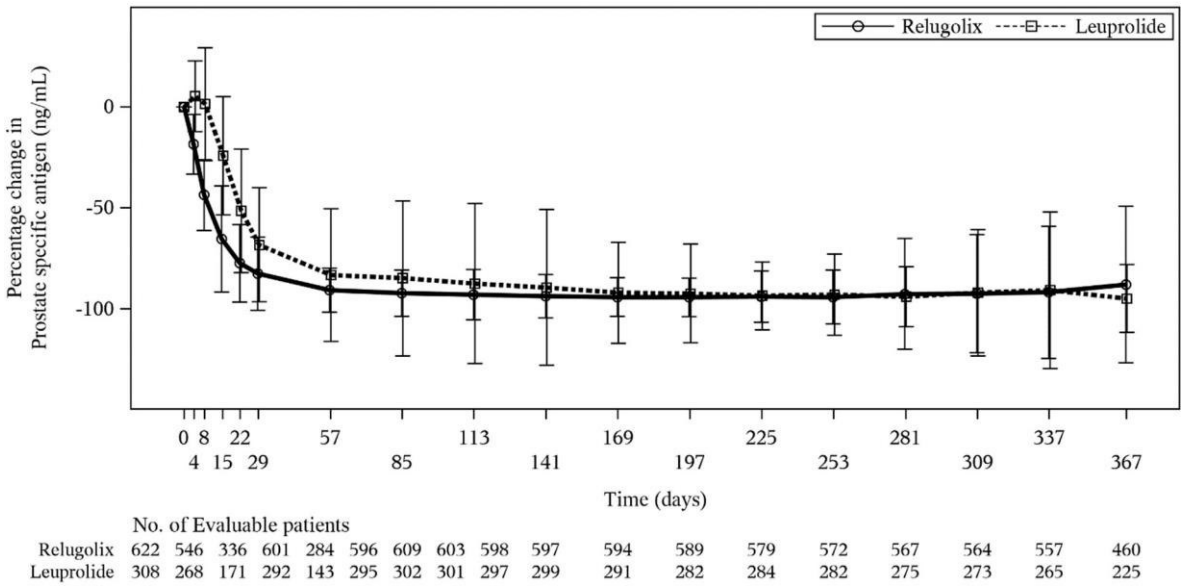
B.2.6.1.7. Prostate-specific antigen related secondary endpoints

PSA-related secondary endpoints included two alpha-protected key secondary endpoint of PSA response at Week 3 Day 1 and Week 5 Day 1, along with other assessments of PSA, PSA response, PSA after discontinuation of treatment, and time to PSA progression.

B.2.6.1.7.a. Prostate-specific antigen levels over time during treatment

PSA concentrations over time are presented in Figure 11.

Figure 11: Percentage Change from Baseline in Prostate-Specific Antigen Concentrations Over Time (mITT Population)



The database lock date was 10 Dec 2019. Abbreviations: mITT = modified intent-to-treat; SD = standard deviation. Mean (+/- SD) are presented.

Patients who received relugolix demonstrated a rapid decrease of PSA compared with an initial increase in PSA in patients who received leuprolide (Figure 11). The decrease in PSA was observed in the relugolix group as early as Week 1 Day 4 (Day 4). Comparatively, in the leuprolide group an increase in PSA was observed. However, by Week 5 Day 1 (Day 29), PSA levels in both groups reached near maximal suppression and continued to be suppressed throughout the study.

Change in PSA concentrations over the first 8 weeks of treatment are presented in Appendix M: Additional clinical evidence (M1.2 **Change from Baseline to Week 8 in Prostate-Specific Antigen**).

B.2.6.1.7.b. Prostate-specific antigen response

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., (64), was an alpha-protected key secondary endpoint. A summary of PSA response status is provided in

Table 16.

Table 16: 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 > 90% reduction from baseline	 498 (80.1) 31 (5.0)	 76.70, 83.14 3.41, 7.00	 62 (20.1) 1 (0.3)	 15.80, 25.05 0.01, 1.80	
Week 5 Day 1 > 50% reduction from baseline > 90% reduction from baseline	 588 (94.5) 251 (40.4)	 92.44, 96.19 36.47, 44.33	 244 (79.2) 61 (19.8)	 74.26, 83.61 15.50, 24.70	
> 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
Week 25 Day 1 < 0.02 ng/mL	 129 (20.7)	 17.62, 24.14	 64 (20.8)	 16.39, 25.74	

The database lock date was 10 Dec 2019. 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)

The proportion of patients with a > 50% reduction in PSA on Week 3 Day 1 (Day 15) confirmed at Week 5 Day 1 (Day 29) was significantly higher in the relugolix group (79.4%) as compared with the leuprolide group (19.8%) ($p < 0.0001$) (

Table 16).

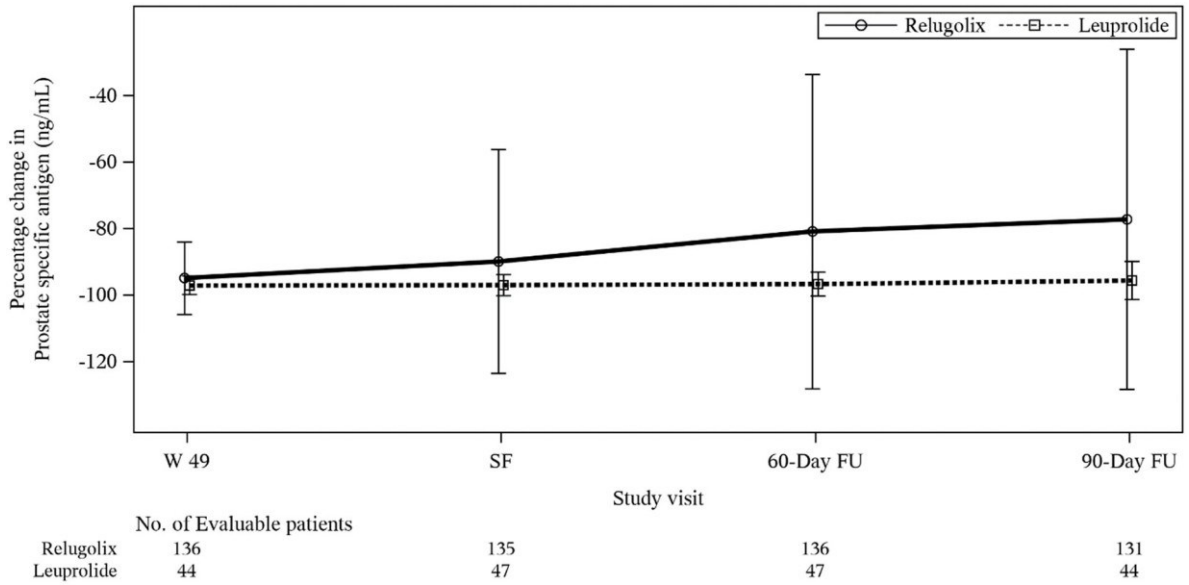
At Week 3 Day 1 (Day 15) and Week 5 Day 1 (Day 29), the proportions of patients with a > 90% reduction in PSA were higher in the relugolix group (5.0% and 40.4%, respectively) as compared with the leuprolide group (0.3% and 19.8%, respectively).

The proportion of patients with PSA concentration < 0.02 ng/mL at the Week 25 Day 1 (Day 169) visit was similar in the relugolix group (20.7%) and in the leuprolide group (20.8%).

B.2.6.1.7.c. Prostate-specific antigen after discontinuation of treatment

The PSA concentration by visit in patients enrolled into testosterone recovery phase are provided in Figure 12.

Figure 12: Percentage Change from Baseline in Prostate-Specific Antigen Concentrations in Testosterone Recovery Phase (mITT Population)



The database lock date was 10 Dec 2019. Abbreviations: FU - follow-up; mITT = modified intent-to-treat; PSA = prostate-specific antigen; SD = standard deviation; SF = safety follow-up. Mean (± SD) are presented.

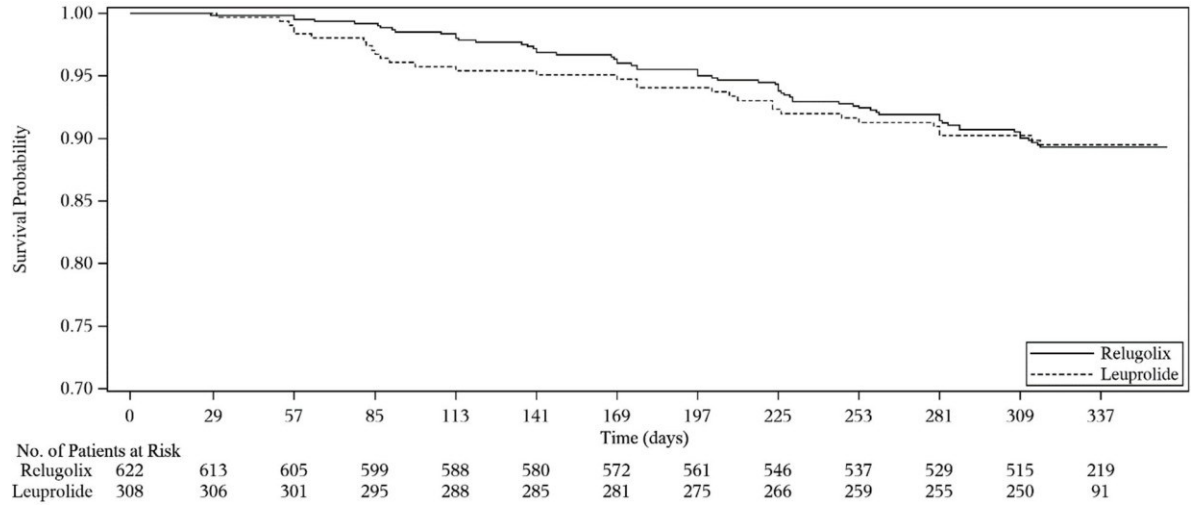
Although there was a small increase in PSA after discontinuation of relugolix (Figure 12), this difference should be interpreted with caution given the wide range of PSA values in the relugolix group caused by outliers. At the 60-day follow-up visit, the mean (SD) PSA values were 4.37 (19.638) ng/mL and 0.63 (2.066) ng/mL in the relugolix and leuprolide groups, respectively, but the median (range) in the relugolix group was 0.33 (0.0 to 180.2) ng/mL compared with 0.04 (0.0 to 13.1) ng/mL in the leuprolide group. At the 90-day follow-up visit, the mean (SD) PSA values were 4.25 (20.901) ng/mL and 0.73 (2.368) ng/mL in the relugolix and leuprolide groups respectively, with the median (range) being 0.39 (0.0 to 233.1) ng/mL and 0.06 (0.0 to 14.0) ng/mL, respectively.

B.2.6.1.7.d. Time to Prostate-Specific Antigen Progression

PSA progression was defined as the first increase in PSA of 25% or greater and 2 ng/mL or greater above the nadir with confirmation by a second consecutive PSA measurement at least 3 weeks later (64). For patients without declining PSA from baseline, a PSA increase of ≥ 25% and ≥ 2 ng/mL from baseline beyond 12 weeks was considered PSA progression.

Kaplan-Meier estimates for time to PSA progression are provided in Figure 13 (Kaplan-Meier curve) and Table 17 (descriptive statistics).

Figure 13: Kaplan-Meier Survival Curve of Time to Prostate-Specific Antigen Progression in All Patients (mITT Population)



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

Table 17: Kaplan-Meier Estimates for Time to Prostate-Specific Antigen Progression (mITT Population)

	Relugolix (N = 622)	**Leuprolide (N = 308)**
Time to PSA progression		
No. of events (%)	63 (10.1)	31 (10.1)
No. of censored (%)	559 (89.9)	277 (89.9)
Median (95% CI)[a]	NE (NE, NE)	NE (NE, NE)
Q1, Q3	NE, NE	NE, NE
Kaplan-Meier estimates on % progression-free rate at Day 337 (95% CI)[a]	89.31 (86.52, 91.55)	89.50 (85.39, 92.50)
Difference from leuprolide (95% CI)[b]	-0.19 (-4.49, 4.11)	
Hazard ratio to leuprolide (95% CI)[c]	0.9932 (0.6459, 1.5272)	
p-value[d]	0.9863/0.9834	
Time to PSA progression-sensitivity analysis[e]		
No. of events (%)	59 (9.5)	23 (7.5)
No. of censored (%)	563 (90.5)	285 (92.5)
Median (95% CI)[a]	NE (NE, NE)	NE (NE, NE)
Q1, Q3	NE, NE	NE, NE
Kaplan-Meier estimates on % progression-free rate at Day 337 (95% CI)[a]	89.84 (87.08, 92.04)	89.71 (84.91, 93.05)
Difference from leuprolide (95% CI)[b]	0.13 (-4.56, 4.82)	
Hazard ratio to leuprolide (95% CI)[c]	0.9527 (0.5883, 1.5428)	
p-value[d]	0.6274/0.6706	

The database lock date was 10 Dec 2019. Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; NE = not estimable; PSA = prostate-specific antigen; Q1 = 25th percentile; Q3 = 75th percentile. Analysis excluded PSA results in the follow-up phase. [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] Hazard ratio in comparison of relugolix to leuprolide is performed using Cox proportional hazard model. [d] p-value is provided using stratified (stratification factors per electronic data capture [primary]/per interactive voice/web recognition system [sensitivity], respectively) log-rank test. [e] As a sensitivity analysis, patients were censored at the time of initiating any antiandrogen/androgen receptor inhibitor in addition to the last available assessment.

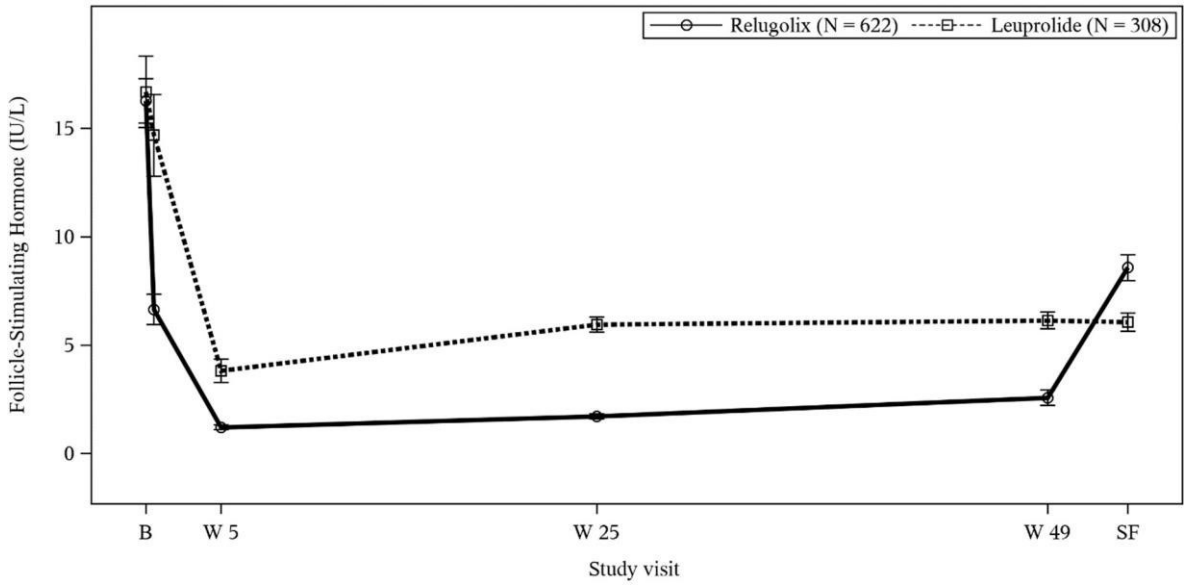
The timing for PSA progression was similar between the treatment groups (Figure 13). A similar proportion of patients had PSA progression in the relugolix and leuprolide groups (10.1% for each group) (Table 17). The rate of progression-free survival at Week 49 Day 1 (Day 337) was similar in both groups, with between-group

difference of -0.19% (95% CI: -4.49%, 4.11%). Similar results were observed in the sensitivity analysis when patients were censored at the time of initiating any medications that could affect or alter PSA level.

B.2.6.1.8. Follicle-Stimulating Hormone Suppression

The FSH concentrations and percent change from baseline in FSH at Week 25 Day 1 was an alpha-protected key secondary endpoint in this study. The FSH concentrations over time are presented by visit in Figure 14.

Figure 14: Follicle-Stimulating Hormone Concentrations Over Time (mITT Population)



The database lock date was 10 Dec 2019. Abbreviations: B = baseline; CI = confidence interval; mITT = modified intent-to-treat; W = week. Mean (95% CI) are presented.

Levels of FSH were suppressed to a greater degree by relugolix than by leuprolide at Week 25 Day 1 (Day 169) (Figure 14), and the difference was statistically significant ($p < 0.0001$). In the relugolix group, the mean (SD) FSH concentration at Week 25 Day 1 (Day 169) 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 at Week 25 Day 1 (Day 169) was 5.95 (3.071) IU/L, with a mean (SD) percent change from baseline of -47.53% (32.560%). This rapid suppression of FSH, to significantly lower concentrations (that were sustained throughout the treatment period), compared to leuprolide could have a benefit in protecting men

from MACE, given prolonged FSH secretion is associated with increased cardiovascular toxicity (65).

B.2.6.1.9. Patient reported outcomes /quality of life

Absolute values and changes from baseline in the scores of each domain in EORTC-QLQ-C30 and EORTC-QLQ-PR25, and the EQ-5D-5L were evaluated at regular intervals during treatment, and during the follow-up, and/or end of treatment. 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 (59). EORTC-QLQ-C30 was not designed specifically to evaluate patients with prostate cancer.

B.2.6.1.9.a. EORTC-QLQ-PR25

Relugolix is an oral GnRH receptor antagonist with rapid testosterone recovery after the drug is withdrawn. Health-related quality of life measures in the testosterone recovery phase, specifically the three domains of hormonal-related symptoms, sexual functioning, and sexual activity, were expected to be superior to leuprolide.

Mean (standard error) score for hormonal treatment-related symptoms domain at the 90-day follow-up visit was lower, indicating less severity of hormonal treatment-related symptoms, in the relugolix group (-4.3 [0.95]) compared with the leuprolide group (0.2 [1.64]), with a between-group difference of -4.5 (95% CI: -8.0, -1.0). Although the clinical significance of this reduction is unclear, the internal consistency of this assessment method has been demonstrated in the literature (66).

There was no significant improvement in either sexual activity or sexual functioning domains between the relugolix group (N=122 and 30, respectively) and the leuprolide group (N=41 and 7, respectively) at the 90-day follow-up. The mean (SD) score of sexual activity was similar between the two groups at the 90-day follow-up visit: 82.5 (21.63) in the relugolix group and 86.2 (22.02) in the leuprolide group. Similarly, the mean (SD) score of sexual functioning was also similar between the two groups at the 90-day follow-up visit: 54.0 (22.13) and 56.0 (16.47) in the relugolix and leuprolide groups, respectively. A possible explanation for the lack of improvement in the sexual functioning domain is the age of patients (mean age =

71.7 years) and the small sample of patients who responded to the assessment throughout the testosterone recovery phase, with only a small proportion of patients in the testosterone recovery subset responding to the questionnaire at the 90-day follow-up in the relugolix (12 patients) and leuprolide group (six patients) (59).

All other domains in the assessment (urinary symptoms, incontinence aid use, and bowel symptoms) were comparable between the two groups.

B.2.6.1.9.b. EQ-5D-5L

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 analogue scores (VAS) were also similar across the two treatment groups.

A similar proportion of patients in the relugolix and leuprolide groups reported no change in mobility (65.2% and 69.8%, respectively), self-care (77.8% and 69.8%, respectively), usual activities (68.1% and 55.8%, respectively), pain discomfort (63.0% and 58.1%, respectively), and anxiety/depression (71.1% and 69.8%, respectively) at the 90-day follow-up visit. Patients in the relugolix and leuprolide groups reported similar median VAS scores (81.0 and 85.0, respectively) at the 90-day follow-up visit. There were no expected differences between the two treatment groups as the questionnaire does not measure prostate cancer-specific quality of life impact.

B.2.6.1.10. Exploratory Endpoints

B.2.6.1.10.a. Overall Survival

During the final weeks prior to database lock, sites attempted to contact all study participants or their immediate family regarding the survival status of previously enrolled/completed study patients. If the site was unsuccessful in contacting the patient and/or immediate family, the site may have accessed hospital records or publicly available sources such as national registries, newspaper obituaries, and social networking websites. During the health status survey, five patients were reported as having died (Table 18).

Table 18: Patients Reported as Dead During the Health Status Survey After the Study

Group	Patient number	Age (years) /Race	Day of last dose	End study Day [a]	Primary cause of death
Relugolix	203303	73/Asian	340	511	Prostate cancer disease progression
	205008	81/White	2	463	Unknown
	208505	75/White	329	449	Unknown
	216701	85/Asian	45	663	Other [b]
Leuprolide	203109	79/White	169	330	Prostate cancer disease progression

The database lock date was 10 Dec 2019. [a] Start/stop day is relative to the date of first dose of study drug in days. [b] Cerebrovascular failure, massive intracerebral haemorrhage at left frontal and parietal lobe with intraventricular haemorrhage and mass effect related. MedDRA Version 22.0.

There were four patients in the relugolix group with deaths reported on the health status survey. Two patients (Patient 205008 and Patient 216701) discontinued early in the study (Day 2 and Day 45, respectively). Patient 205008 was lost to follow up and therefore discontinued from the study. Patient 216701 discontinued from the study on Day 45 after a serious adverse events of acute lacunar infarction, infective endocarditis with vegetations, and septic shock. The other two patients (Patient 203303 and Patient 208505) completed the 48 weeks of treatment; Patient 203303 died of prostate cancer progression and the cause of death for Patient 208505 was unknown. One patient in the leuprolide group (Patient 203109) had death from prostate cancer progression reported on the health status survey. There were eight patients whose survival status was unknown. The median follow-up time of patients in the health status survey was 463.5 days in the relugolix group and 456.5 days in the leuprolide group.

Overall survival was defined as time from randomization to date of death prior to the data-cut off. Result of the analysis are provided in Table 19.

Table 19: Kaplan-Meier Estimates for Overall Survival (mITT Population)

	Relugolix (N = 622) [a]	**Leuprolide (N = 308)**
Overall Survival		
No. of events (%)	12 (1.9)	10 (3.2)
No. of censored (%)	610 (98.1)	298 (96.8)
Median (95% CI) [a]	NE (NE, NE)	NE (NE, NE)
Q1, Q3	NE, NE	NE, NE
Kaplan-Meier estimates on survival rate at Day 337 (95% CI)[a]	0.9885 (0.9761, 0.9945)	0.9740 (0.9486, 0.9869)
Difference from leuprolide (95% CI)[b]	0.0146 (-0.0051, 0.0343)	
Hazard ratio from leuprolide (95% CI)[c]	0.5957 (0.2574, 1.3787)	
Follow-up time in days		
Median	463.5	456.5
Q1, Q3	376.0, 562.0	377.5, 568.5
No. of patients with unknown status at the health status follow-up, n (%)	6 (1.0)	2 (0.6)

The database lock date was 10 Dec 2019. Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; NE = not estimable; Q1 = 25th percentile; Q3 = 75th percentile. [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] Hazard ratio in comparison of relugolix to leuprolide was performed using Cox proportional hazard model.

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) (Table 19).

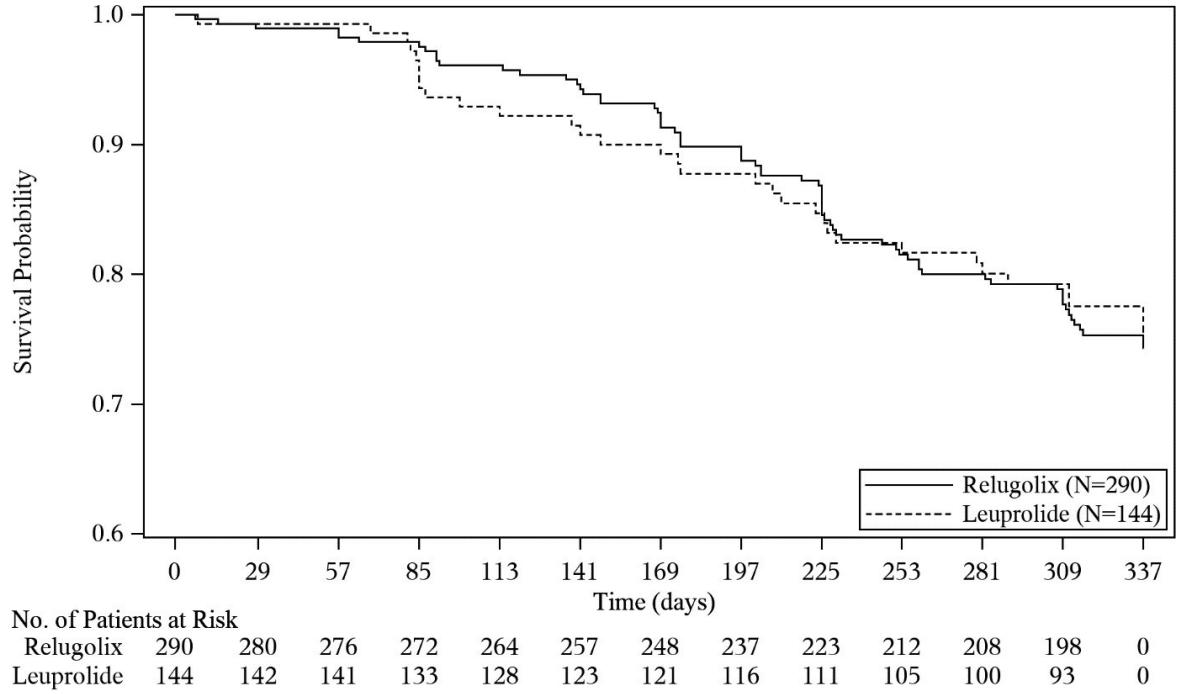
The 22 deaths in the overall survival analysis comprise the 16 patients who died due to a treatment-emergent adverse event during the study (seven in the relugolix arm and nine in the leuprolide arm), one patient in the relugolix arm who died after the adverse event reporting period, and five patients (four in the relugolix arm and one in the leuprolide arm; Table 18), reported during the health status survey as having died after the study and before database lock.

B.2.6.1.10.b. Castration resistance-free survival.

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). The

Kaplan-Meier survival curve of CRFS in metastatic patients is provided in Figure 15 and the Kaplan-Meier estimates are provided in Table 20.

Figure 15: Kaplan-Meier Survival Curve of CRFS in Metastatic Patients



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 CRFS in Metastatic Patients (mITT Metastatic Patient Population)

	Relugolix (N = 290) [a]	**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 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	

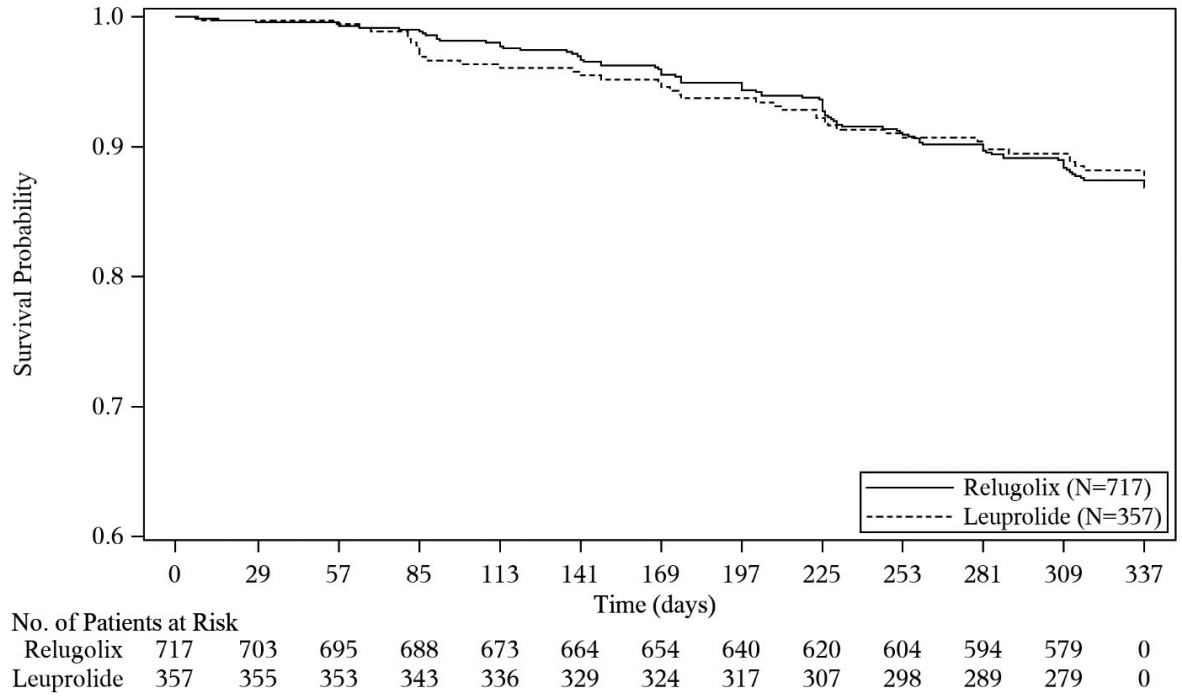
The database lock date was 23 Sep 2020. Abbreviations: CI = confidence interval; EDC = electronic data capture; IWRS = interactive voice/web recognition system; mITT = modified intent-to-treat; N =

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, 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 significance and was thus analysed as exploratory.

The Kaplan-Meier survival curve of CRFS in all patients is provided in Figure 16. and the Kaplan-Meier estimates are provided in Table 21.

Figure 16: Kaplan-Meier Survival Curve of CRFS in All Patients (With and Without Metastatic Disease) (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 CRFS in All Patients (mITT Final Analysis Population)

	Relugolix (N = 717) [a]	**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)	
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.

B.2.6.2. CS7003 clinical evidence

The primary endpoint for this study was the rate of effective castration, between 4 and 24 weeks of treatment, defined as the estimated proportion of patients with testosterone concentrations <1.73 nmol/l (<50 ng/dl) at all scheduled visits. A lower (profound) castration threshold was defined as testosterone levels <0.7 nmol/l (<20 ng/dl). Secondary endpoints included PSA response at 12 weeks and PSA nadir during treatment and follow-up, and the time to achieve effective castration and testosterone recovery (recovery was defined as the return of testosterone values to baseline or to >9.8 nmol/l [>280 ng/dl]).

B.2.6.2.1. ***Castration rates***

Castration rates over 24 weeks with relugolix and degarelix are shown in Table 22 (53). Treatment with either relugolix or degarelix was associated with high rates of effective castration, with castration rates (<50 ng/dL) of 95% and 89%, respectively.

The profound castration rates for the lower threshold of 0.7 nmol/l (20 ng/dl) were 82% in the relugolix group and 68% in the degarelix group.

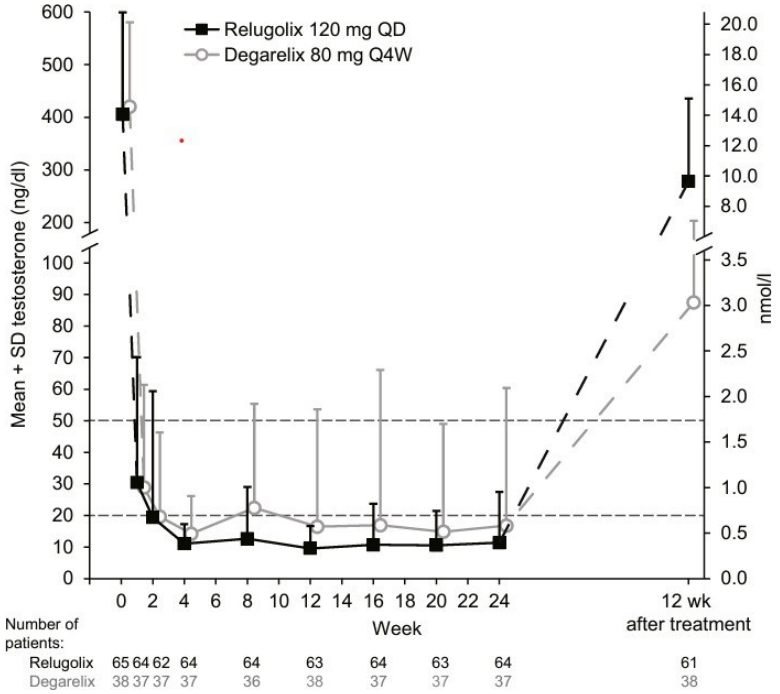
Table 22: C27003 Trial: Castration Rates for Patients Who Received at Least One Dose of Treatment

	Relugolix 120 mg QD (N = 65) [a]	**Degarelix 80 mg Q4W (N = 38)**
Castration rate[a] over 24 weeks n (%) 95% CI[b] (two-sided)	 62 (95) 87.1-99.0	 34 (89) 75.2-97.1
Profound castration rate[c] over 24 weeks n (%) 95% CI[b] (two-sided)	 53 (82) 70.0-90.1	 26 (68) 51.3-82.5

CI=confidence interval; Q4W=once every 4 weeks; QD=once daily. [a] Castration rate was defined as the estimated proportion of patients with testosterone concentrations <50 ng/dL at all scheduled visits from Week 4 through Week 24. [b] The two-sided 95% CIs were calculated using the exact method. [c] Profound castration rate was defined as the estimated proportion of patients with testosterone concentrations. <20 ng/dL at all scheduled visits from Week 13, Day 1 through to Week 25, Day 1.

Mean testosterone levels across 24 weeks of treatment and 12 week of follow-up after discontinuation of treatment are reported in Figure 17. The time to castration was rapid in both groups, at a median of 4 days in the relugolix group and 3 days in the degarelix group. Following discontinuation of relugolix treatment at 24 weeks, testosterone levels recovered rapidly within 12 weeks; recovery to baseline or >9.8 nmol/l (280 ng/dl) occurred in 52% of patients. In the degarelix group, median testosterone remained well below 1.73 nmol/l (<50 ng/dl) following discontinuation, with only 16% of patients meeting the protocol-specified definition of testosterone recovery to baseline or >9.8 nmol/l.

Figure 17: Mean Testosterone Levels through Week 24 and after treatment discontinuation



Mean (+SD) testosterone levels are presented over time, including during treatment (24 wk) and during 12 wk of follow-up after study drug discontinuation. Note the break in the y axis and different scaling of values <100 versus >200 ng/dl. Data for the two treatment arms are staggered along the x axis for legibility. The dotted lines indicate a castration threshold of 1.73 nmol/l (50 ng/dl) or 0.7 nmol/l (20 ng/dl). The week-2 assessment in one patient in the relugolix group is omitted from this figure as the value was 10 times the upper limit of normal and is believed to be a technical error. All other data from this patient are included in the analysis. QD = once daily; Q4W = once every 4 wk; SD = standard deviation.

B.2.6.2.2. PSA response and suppression of FSH

In both groups, median PSA levels steadily declined through Week 24. Percentage responses in PSA reduction are shown in Table 23. By week 12, the reduction in PSA by 50% in both groups was 97%, and the reduction in PSA by 90% was 55% and 47% in the relugolix and degarelix groups, respectively.

Table 23:C27003 Trial: Percentage Responses in Prostate Specific Antigen Reduction

	PSA Reduction by ≥50%		PSA Reduction by ≥90%	
	Relugolix [a]	Degarelix	Relugolix	Degarelix
Week 12	98%	97%	55%	47%
Week 24	98%	100%	95%	92%

PSA = Prostate specific antigen

Median PSA levels remained low after treatment discontinuation in both arms (Table 24). FSH levels were suppressed on treatment with both relugolix and degarelix, to a similar extent.

Table 24: Suppression of FSH, and testosterone from baseline to the end of treatment (week 24), and recovery through week 36, with associated PSA levels

	Relugolix 120 mg QD (N = 65)			Degarelix 80 mg Q4Q (N = 38)		
	FSH, IU/dL	**Testosterone, ng/dL**	**PSA µg/L**	**FSH, IU/dL**	**Testosterone, ng/dL**	**PSA µg/L**
Baseline	6.7 (5.2,10.7)	355.7 (283.7, 469.7)	7.3 (5.0, 12.3)	7.5 (5.2, 14.5)	403.8 (289.7, 509.8)	7.3 (5.5, 11.2)
Week 24	0.8 (0.3, 1.5)	8.1 (5.6, 10.9)	0.1 (0.1, 0.2)	0.7 (0.3, 1.6)	8.9 (5.2, 13.0)	0.1 (0.1, 0.2)
Week 28	6.3 (4.0, 9.9)	93.9 (34.8, 205.9)	0.1 (0.1, 0.3)	1.3 (0.7, 2.7)	9.6 (6.6, 13.0)	0.1 (0.1, 0.1)
Week 36	[a]	256.9 (191.8, 342.7)	0.2 (0.1, 0.5)	[a]	30.0 (10.1, 123.0)	0.1 (0.1, 0.2)

FSH = follicle stimulating hormone; LH = luteinizing hormone; PSA = prostate-specific antigen; Q4W = once every 4 weeks; QD = once daily. Values are expressed as median (interquartile range). [a]Not assessed at this time point per pre-specified schedule of study procedures.

B.2.7. Subgroup analysis

B.2.7.1. Subgroup analysis for the primary effect endpoint

Subgroup analyses were conducted for geographic region, age, race, ethnicity, baseline testosterone and PSA levels, clinical disease state at screening, Gleason score, and the presence of metastatic disease. The results of the subgroup analyses for Evaluation Criterion 1 (sustained castration rate) and Evaluation Criterion 2 are presented in Appendix E: Subgroup analysis.

Across all subgroups, point estimates for sustained castration rates for relugolix patients were consistent with the overall estimate of relugolix sustained castration rate observed for Evaluation Criterion 1 (relugolix castration rate > 90%). In addition, the lower bounds of the 95% CI for the relugolix sustained castration rate exceeded 90% except for the comparatively smaller subgroups of Black or African American (N = 46) and Hispanic or Latino patients (N = 83) and the majority of the CIs for the difference in rates excluded zero, consistently favouring relugolix.

Across all subgroups, except for the subgroup of Black or African American patients, differences in sustained castration rates were consistent with the overall difference observed for Evaluation Criterion 2. In addition, the lower bound of the 95% CI for the difference in the sustained castration rate between the two treatment groups was greater than the noninferiority margin of -10% except for the comparatively smaller subgroup of Black or African American patients, and above zero for most subgroups consistent with the demonstration of superiority of relugolix to leuprolide observed from the overall population.

B.2.7.2. Subgroup analysis of patients receiving concomitant enzalutamide and docetaxel

In a subset of patients whose disease progressed during the HERO study, enzalutamide or docetaxel was prescribed in accordance with prostate cancer treatment guidelines. The study was published in Clinical Genitourinary Cancer, in 2023 (57), and a summary of the results is presented below and in Appendix E: Subgroup analysis.

Overall, 156 patients (14.6%) took concomitant therapies that could impact testosterone levels (Table 80, Appendix E: Subgroup analysis, section E.1. 2). Enzalutamide (n = 20) was the most frequently used therapy in the relugolix (2.8%) and leuprolide groups (2.5%). Docetaxel (n = 28) was used by 2.4% and 3.1% of patients in the relugolix and leuprolide groups, respectively. All other relevant concomitant therapy were used in < 1% of the population.

Sensitivity analysis showed concomitant therapy did not impact the testosterone levels (Figure 32, & Table 81, Appendix E: Subgroup analysis). Castration rates were similar with and without concomitant use of enzalutamide or docetaxel. No clinically relevant differences in adverse events were observed between subgroups in either treatment group (Table 82, Appendix E: Subgroup analysis). Hot flash was the most common adverse event in both groups (relugolix: with enzalutamide [ENZ], 65.0%; with docetaxel [DOC], 70.6%; overall, 53.8%; leuprolide: with ENZ, 44.4%; with DOC, 45.5%; overall, 51.0). Diarrhoea was reported in a higher percentage of patients in the relugolix group (with ENZ, 10.0%; with DOC, 11.8%; overall, 11.4%) than in the leuprolide group (with ENZ, 0%; with DOC, 9.1%; overall, 6.4%). All

cases of diarrhoea were mild or moderate in intensity (grade 1 or grade 2), and no patient was withdrawn because of diarrhoea. As expected, concomitant therapy with enzalutamide or docetaxel was associated with a higher frequency of serious and fatal AEs in both treatment groups, although patient numbers were too small to make any definitive conclusions.

In summary, men who received concomitant administration of enzalutamide or docetaxel demonstrated similar testosterone suppression to patients on relugolix alone. Overall incidence of adverse events was similar between relugolix and leuprolide in patients with or without concomitant therapy. Serious adverse events including death were generally more frequent in patients taking combination therapy in both treatment groups likely reflecting the more advanced disease and the safety profile of added therapies...

B.2.8. Meta-analysis

Not applicable.

B.2.9. Indirect and mixed treatment comparisons

B.2.9.1. Summary of trials

As the HERO study compared relugolix to leuprolide, all other studies using leuprolide as an intervention or comparator were assessed for their similarity to the HERO study in terms of the dosing and frequency of administration of leuprolide.

Among the 28 RCTs identified by the SLR, 19 reported information on at least one outcome of interest; 10 evaluated testosterone suppression (TS) to castrate levels defined as testosterone <50 ng/dL(60, 67-75); 3 evaluated PSA response defined as a ≥50% reduction in PSA from baseline (68, 71, 74); 2 evaluated time to PSA progression using a similar definition (PSA ≥25% and ≥2ng/mL) (71, 76); 11 reported Kaplan-Meier curves for Overall Survival (OS) (67, 76-83); and 2 reported information on MACE and/or CV related events (60, 71). Among these 19 RCTs, 5 were eligible for the NMA (60, 69, 71-73); 14 were excluded, one of which was a Phase 2 study (68) and 13 did not facilitate an indirect comparison against a comparator of interest.

Ultimately, 5 studies with potentially comparable leuprolide dosing were assessed for similarity in terms of outcome definitions and timepoints. These studies could facilitate an indirect comparison via leuprolide between relugolix and degarelix, goserelin, and triptorelin, although the differences in the reported outcome timepoints limit the viability of these indirect comparisons. A full description of the methodology of the indirect treatment comparison is provided in Appendix D: Identification, selection and synthesis of clinical evidence. The selected trials and the interventions studied are summarised in Table 25.

Table 25: Summary of the trials used to carry out the indirect treatment comparison

Study Name	Relugolix	Leuprolide	Degarelix	Triptorelin	Goserelin
HERO	Yes	Yes			
Heyns 2003		Yes		Yes	
Silva 2012		Yes			Yes
Tanaka 2007		Yes			Yes
CS21 / CS21 A (OLE)		Yes	Yes		

B.2.9.2. Results

Outcome definitions from each of the 6 studies were compared to those in the HERO study. Six outcomes from the HERO study were found to be potentially comparable to at least 1 outcome from the 6 studies. The 6 outcomes were:

- Cumulative probability of testosterone suppression to <50 ng/dl
- Cumulative probability of profound testosterone suppression to <20 ng/dl
- Mean testosterone levels
- PSA response
- FSH level
- Withdrawals due to adverse events

In summary, it was determined that NMAs assessing the efficacy and safety of treatments for HSPC were feasible for two outcomes: Testosterone suppression to castrate levels (<50ng/dL) and MACE or CV-related events.

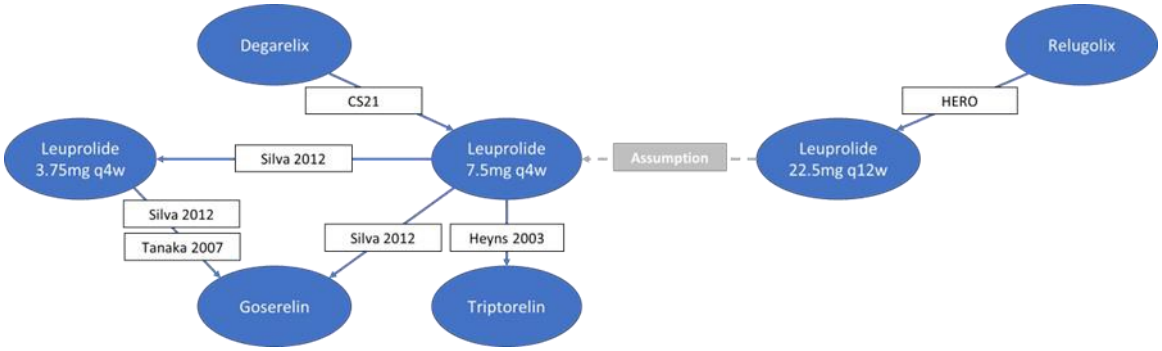
B.2.9.2.1. NMA of testosterone suppression to castrate levels

Five eligible studies reported information on TS to castrate levels. The threshold for castration levels of testosterone, <50 ng/dL, was chosen to reflect the threshold used in the HERO trial. In the HERO trial, testosterone castration was assessed after approximately 11 months, and 12 months in the CS21 trial (38, 60). In both studies, castration was based on the cumulative probability of castration from day 28 until end of study (11 and 12 months, respectively). The remaining studies assessed castration rates much sooner. Investigators in the Silva 2012 study assessed TS at 3 months compared to 2 months in the Heyns 2003 study (69, 84).. In the Tanaka 2007 study, TS was assessed at 1 month (73). Full details of the criteria are presented in Table 16, Appendix D, section D.1.3.1.

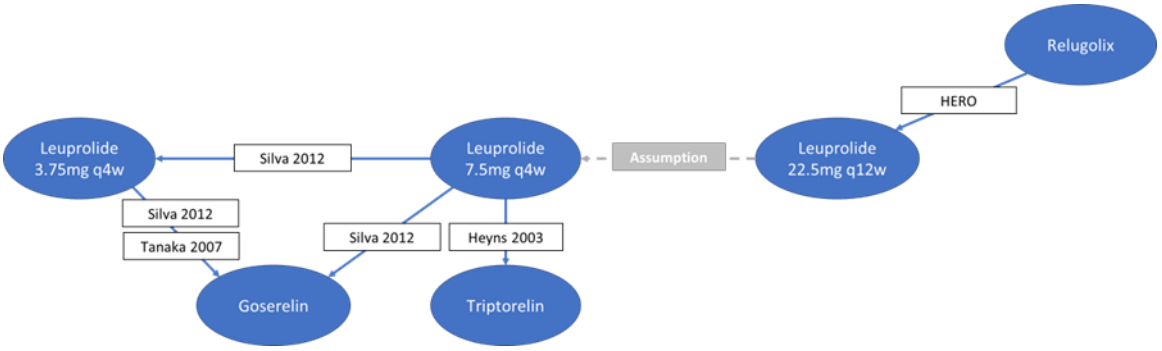
The evidence network for the NMA of testosterone suppression to castrate levels is shown in Figure 18. It was assumed that the leuprolide 7.5mg Q4W is equivalent to leuprolide 22.5mg Q12W as it is otherwise not possible to connect relugolix 120mg to any of the evidence networks.

Figure 18: Network diagram for NMA of testosterone suppression

A. Primary Analysis



B. Sensitivity Analysis



The network diagram for NMA of testosterone suppression. A. Primary Analysis. B Sensitivity analysis in which degarelix was excluded from the evidence network.

Raw data on testosterone suppression to castrate levels (<50ng/dL) from RCTs of treatment for HSPC are summarised in Table **26**.

Table 26**: Individual study data for testosterone suppression**

Study Name	Treatment Name											
	Relugolix		Degarelix		Triptorelin		Goserelin		Leuprolide 3M		Leuprolide 1M	
	n	N	n	N	n	N	n	N	n	N	n	N
HERO (38)	601	622							274	308		
CS21 (60)			202	207					194	201		
Heyns 2003 (69)					130	132			135	139		
Tanaka 2007 (73)							11	11			10	11
Silva 2012 (72)							13	20	15	20	14	20

*Removed study and degarelix for sensitivity analysis; n = number of events; N = total number of patients; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

B.2.9.2.1.a. Results of evidence synthesis for testosterone suppression

Estimated treatment effects expressed as odds ratios (ORs) and relative risks (RRs) are presented in league tables (Table 27 and Table 28) for the best-fitting model: random effects hierarchical NMA with informed priors. There were no statistically significant differences between relugolix versus degarelix or triptorelin, as the 95% confidence interval (CI) for these ORs contained the value 1.0. Relugolix had a significant benefit on achieving testosterone suppression to castrate levels

(<50ng/dL) compared with leuprolide 22.5mg Q12W/7.5mg Q4W (OR = 2.89; 95% CI: 1.46 6.57), goserelin (OR = 2.81; 95% CI: 1.08, 12.67), and leuprolide 3.75mg Q4W (OR = 2.85; 95% CI: 1.12, 13.05). For other comparators, there were no statistically significant differences in achieving testosterone suppression to castrate levels.

Table 27: League table for odds ratios of testosterone suppression to castrate levels: Primary analysis Including degarelix

Relugolix	0.84 (0.20, 1.69)	0.47 (0.11, 1.48)	0.35 (0.15, 0.68)	0.36 (0.08, 0.92)	0.35 (0.08, 0.89)
1.19 (0.59, 4.94)	**Degarelix**	0.78 (0.14, 3.18)	0.51 (0.16, 1.39)	0.53 (0.11, 1.71)	0.51 (0.11, 1.70)
2.13 (0.68, 8.94)	1.28 (0.31, 7.25)	**Triptorelin**	0.97 (0.24, 2.15)	0.95 (0.16, 2.21)	0.94 (0.15, 2.23)
2.89 (1.46, 6.57)	1.98 (0.72, 6.15)	1.03 (0.47, 4.11)	**Leuprolide 3M**	0.82 (0.32, 2.22)	1.01 (0.32, 2.17)
2.81 (1.08, 12.67)	1.87 (0.58, 9.43)	1.06 (0.45, 6.35)	1.21 (0.45, 3.10)	**Goserelin**	1.09 (0.39, 2.50)
2.85 (1.12, 13.05)	1.96 (0.59, 9.46)	1.07 (0.45, 6.46)	0.99 (0.46, 3.15)	0.92 (0.40, 2.58)	**Leuprolide 1M**

Yellow boxes indicate statistical significance; clear boxes indicate no statistical significance;

Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

Table 28: League table for relative risks of testosterone suppression to castrate Levels: Primary analysis Including degarelix

Relugolix	0.99 (0.91, 1.01)	0.95 (0.83, 1.01)	0.95 (0.87, 0.99)	0.93 (0.77, 1.00)	0.93 (0.77, 1.00)
1.01 (0.99, 1.10)	**Degarelix**	0.96 (0.85, 1.06)	0.96 (0.89, 1.02)	0.95 (0.80, 1.03)	0.95 (0.80, 1.03)
1.05 (0.99, 1.20)	1.04 (0.95, 1.17)	**Triptorelin**	1.00 (0.93, 1.09)	0.98 (0.83, 1.07)	0.98 (0.83, 1.07)
1.06 (1.01, 1.14)	1.04 (0.98, 1.12)	1.00 (0.91, 1.08)	**Leuprolide 3M**	0.98 (0.85, 1.05)	0.99 (0.84, 1.05)
1.07 (1.00, 1.29)	1.06 (0.97, 1.25)	1.02 (0.93, 1.20)	1.02 (0.95, 1.18)	**Goserelin**	1.00 (0.89, 1.11)
1.07 (1.00, 1.30)	1.06 (0.97, 1.26)	1.02 (0.93, 1.21)	1.01 (0.95, 1.19)	1.00 (0.90, 1.12)	**Leuprolide 1M**

Yellow boxes indicate statistical significance; clear boxes indicate no statistical significance;
Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

B.2.9.2.1.b. Sensitivity analysis for testosterone suppression

A sensitivity analysis was conducted in which degarelix was excluded from the evidence network. While degarelix is licensed as a treatment for patients with advanced HSPC in the UK, NICE recommends it as an option only for a subset of these patients with spinal metastases (26). Therefore, a sensitivity analysis was conducted excluding degarelix from the network to assess the impact of its exclusion.

Estimated ORs and RRs of treatments in the sensitivity analysis without degarelix are shown in Table 29 and Table 30, respectively for the random effects hierarchical NMA with informed priors. While the hierarchical NMA with vague priors had better fit based on deviance information criterion (DIC), we presented the same model type for the sensitivity analysis based on the best-fitting model from the primary analysis. In the NMA with degarelix excluded, there were no statistically significant differences between relugolix and triptorelin. goserelin, or leuprolide 3.75mg Q4W; relugolix did have a significant benefit versus leuprolide 22.5mg Q12W/7.5mg Q4W (OR = 2.69; 95% CI: 1.19, 6.90).

Table 29: League table for odds ratios of testosterone suppression without degarelix

Relugolix	0.95 (0.14, 2.94)	0.60 (0.07, 1.44)	0.37 (0.15, 0.84)	0.39 (0.06, 1.14)
1.05 (0.34, 7.06)	**Triptorelin**	0.87 (0.07, 2.65)	0.61 (0.11, 1.95)	0.64 (0.06, 2.42)
1.68 (0.70, 13.98)	1.15 (0.38, 13.93)	**Goserelin**	1.04 (0.23, 3.58)	0.90 (0.20, 2.85)
2.69 (1.19, 6.90)	1.63 (0.51, 9.02)	0.96 (0.28, 4.26)	**Leuprolide 3M**	1.06 (0.24, 2.73)
2.57 (0.87, 16.59)	1.57 (0.41, 16.43)	1.11 (0.35, 4.97)	0.95 (0.37, 4.12)	**Leuprolide 1M**

Yellow boxes indicate statistical significance; clear boxes indicate no statistical significance;

Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

Table 30: League table for relative risks of testosterone suppression without degarelix

Relugolix	0.98 (0.87, 1.02)	0.95 (0.76, 1.01)	0.95 (0.87, 1.00)	0.93 (0.72, 1.00)
1.02 (0.98, 1.15)	**Triptorelin**	0.97 (0.79, 1.07)	0.97 (0.89, 1.07)	0.95 (0.75, 1.06)
1.05 (0.99, 1.32)	1.03 (0.94, 1.27)	**Goserelin**	1.00 (0.92, 1.21)	0.98 (0.83, 1.13)
1.06 (1.00, 1.15)	1.03 (0.94, 1.12)	1.00 (0.82, 1.09)	**Leuprolide 3M**	0.98 (0.79, 1.06)
1.08 (1.00, 1.39)	1.05 (0.94, 1.33)	1.02 (0.89, 1.20)	1.02 (0.94, 1.26)	**Leuprolide 1M**

Yellow boxes indicate statistical significance; clear boxes indicate no statistical significance;

Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

B.2.9.2.1.c. Model fit

To assess model fit, we compared the DIC for random effects models with individual treatment effects only and hierarchical frameworks as well as vague priors and informative priors. The following model fits for testosterone suppression to castrate levels are shown in Table 31. The hierarchical models appeared to have slightly better fit, demonstrated by the lower DIC values, compared with the models that considered individual treatment effects only. The best-fitting model was the

hierarchical random effects model with informed priors. As such, this model was preferred for the primary analysis of testosterone suppression to castrate levels.

Table 31: Model Fit for NMA of testosterone suppression to Castrate Levels: Primary Analysis

Random Effects Model	Treatment Effects	DIC
Informed Priors	Individual only	57.0
Vague Priors	Individual only	56.1
Informed Priors	**Hierarchical**	**53.4**
Vague Priors	Hierarchical	54.3

DIC: deviance information criterion

Goodness of Fit for the models in the sensitivity analysis is summarised in Table 32. The best fitting model for the NMA network with degarelix excluded was the random effects hierarchical NMA with vague priors, as demonstrated by having the lowest DIC value.

Table 32: Model Fit for NMA of testosterone suppression to Castrate Levels: Sensitivity Analysis

Random Effects Model	Treatment Effects	DIC
Informed Priors	Individual only	45.6
Vague Priors	Individual only	45.1
Informed Priors	**Hierarchical**	**45.4**
Vague Priors	Hierarchical	44.8

DIC: deviance information criterion; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

B.2.9.2.1.d. Treatment ranking for testosterone suppression.

The SUCRA ranking for testosterone suppression to castrate levels (<50ng/dL) is shown in Table 33, which ranks the treatments based on probability of having the best efficacy: relugolix ranked 1st (SURCRA = 0.92), followed by degarelix (SUCRA = 0.78), and triptorelin (SUCRA = 0.41).

Table 33: SUCRA Ranking for testosterone suppression to Castrate Levels: Primary Analysis

Treatment	SUCRA
Relugolix	0.9211
Degarelix	0.7778
Triptorelin	0.4131
Leuprolide 3M	0.3191
Goserelin	0.2870
Leuprolide 1M	0.2819

SUCRA: surface under the cumulative ranking; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

The SUCRA ranking for testosterone suppression to castrate levels (<50ng/dL) based on the sensitivity analysis (excluding degarelix) is shown in Table 34 Similar to the primary analysis, relugolix ranked 1st (SUCRA = 0.8793). With degarelix excluded from the network, triptorelin ranked 2nd (SUCRA = 0.6860) followed by leuprolide 22.5mg Q12W/7.5mg Q4W.

Table 34: SUCRA Ranking for testosterone suppression without degarelix

Treatment	SUCRA
Relugolix	0.8793
Triptorelin	0.6860
Leuprolide 3M	0.4448
Goserelin	0.2611
Leuprolide 1M	0.2288

SUCRA: surface under the cumulative ranking; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

B.2.9.2.2. NMA of Major CV-related events (MACE)

Among the 5 eligible RCTs identified by the SLR, two studies reported information on MACE or CV-related events, HERO and CS21 (60, 71, 85). In HERO, MACE was a composite outcome defined as non-fatal myocardial infarction (MI), non-fatal stroke, ischemic heart disease (IHD), other-non-fatal CV events (i.e., carotid arteriosclerosis and transient ischemic attacks), and fatal CV-related events (data on file, (59)). For the purposes of these analyses, only CV related deaths were included in MACE.

In the CS21 trial, information was available on numbers of CV-related events including stroke, IHD, and fatal CV-related events (85). After the SLR was conducted, it was determined that an additional study by Margel (2019) was omitted from the search due to an indexing error but would have met eligibility criteria for the NMA (7). As such, this study was added to the evidence base for the NMA of MACE and CV-related events. In the Margel 2019 study, degarelix was evaluated for endothelial function and CV-related events versus non-specific (i.e., clinician-preferred regimen) treatment with a GnRH agonist (7). For the purposes of the NMA, the control arm was assumed to be leuprolide so that a connected NMA network could be constructed with the other therapies. A full description of the definitions of

MACE is presented in Table 17, Appendix D: Identification, selection and synthesis of clinical evidence,.

The evidence network for the MACE outcome is shown in Figure 19. As in the testosterone suppression network, it was assumed that the leuprolide 7.5mg Q4W is equivalent to leuprolide 22.5mg Q12W as it is otherwise not possible to connect relugolix 120mg to any of the evidence networks.

Figure 19: Network diagram for NMA of MACE

The individual study data for MACE and CV-related events are shown in **Table 35**. There could only be a connected network by assuming equivalency of leuprolide 22.5mg Q12W and leuprolide 7.5mg Q4W.

Table 35: Individual Study Data for MACE events

	Treatment Name					
Study Name	**Leuprolide**		**Relugolix**		**Degarelix**	
	n	**N**	**n**	**N**	**n**	**N**
HERO (86)	19	308	18	622		
CS21 (85)	27	201			30	409
*Margel 2019 (7)	13	39			2	41

*Included study for sensitivity analysis only; n = number of events; N = total number of patients; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

B.2.9.2.2.a. Results of evidence synthesis for MACE

Estimated treatment effects expressed as ORs and RRs are presented in the league tables for the random effects model with individual treatment effects only and informed priors (Table 36 and Table 37). Results of the NMA suggest there are no statistically significant differences in terms of MACE or CV-related events between relugolix versus either of the other comparators.

Table 36: League table for odds ratios of MACE: Primary analysis

Degarelix	1.03 (0.38, 5.19)	3.17 (1.38, 7.28)
0.97 (0.19, 2.61)	**Relugolix**	2.55 (0.81, 6.20)
0.32 (0.14, 0.72)	0.39 (0.16, 1.23)	**Leuprolide**

Yellow boxes indicate statistical significance (credible interval >1); clear boxes indicate no statistical significance; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

Table 37: League table for relative risks of MACE: Primary analysis

Degarelix	1.06 (0.40, 5.07)	3.01 (1.36, 6.79)
0.94 (0.20, 2.49)	**Relugolix**	2.37 (0.81, 5.39)
0.33 (0.15, 0.74)	0.42 (0.19, 1.23)	**Leuprolide**

Yellow boxes indicate statistical significance (credible interval >1); clear boxes indicate no statistical significance; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

B.2.9.2.2.b. Sensitivity analysis for MACE

A sensitivity analysis was conducted in which data from the Margel study was excluded from the evidence network. As mentioned above, the control arm in Margel (2019) was a non-specific GnRH agonist treatment (based on clinicians' discretion) which was assumed to be leuprolide in the primary analysis. This may have biased the results to the extent that effects of different GnRH agonists on MACE and/or CV-related events may vary. The sensitivity analysis allowed for assessment of how the results were impacted by the exclusion of the Margel 2019 study (7).

Estimated treatment effects expressed as ORs and RRs are presented in the league tables (Table 38 and Table **39,** respectively) for the random effects model with individual treatment effects only and informed priors. Results of the NMA suggest there are no statistically significant differences in terms of MACE or CV-related events between any of the other comparators.

Table 38: League table for odds ratios of MACE: Sensitivity analysis without Margel

Relugolix	1.42 (0.33, 3.81)	2.47 (0.89, 5.43)
0.70 (0.26, 3.04)	**Degarelix**	2.18 (0.86, 4.49)
0.41 (0.18, 1.13)	0.46 (0.22, 1.17)	**Leuprolide**

Yellow boxes indicate statistical significance (credible interval >1); clear boxes indicate no statistical significance; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

Table 39**: League table for relative risks of MACE: Sensitivity analysis without Margel**

Relugolix	1.02 (0.61, 1.32)	1.20 (0.96, 1.38)
0.98 (0.76, 1.65)	**Degarelix**	1.22 (0.98, 1.74)
0.84 (0.72, 1.04)	0.82 (0.58, 1.02)	**Leuprolide**

Yellow boxes indicate statistical significance (credible interval >1); clear boxes indicate no statistical significance; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

B.2.9.2.2.c. Model fit for NMA of MACE

To assess model fit, we compared the DIC for random effects models with individual treatment effects only and hierarchical frameworks as well as vague priors and informative priors. Goodness of fit statistics for the primary analysis of MACE and CV-related events are shown in Table **40**. The hierarchical NMA models had poorer fit compared with the models that considered individual treatment effects only. The best-fitting model was the random effects NMA with vague priors. However, the random effects model with informed priors was preferred since this model is associated with less uncertainty and may produce narrower credible intervals for the treatment effects (87).

Table 40**: Model fit for NMA of MACE: Primary analysis**

Random Effects Model	Treatment Effects	DIC
Informed Priors	**Individual only**	**39.6**
Vague Priors	Individual only	38.1

Random Effects Model	Treatment Effects	DIC
Informed Priors	Hierarchical	44.1
Vague Priors	Hierarchical	42.3

DIC: deviance information criterion

B.2.9.2.2.d. Treatment Ranking for MACE

SUCRA values for the NMA of MACE based on the primary analysis (individual with informed priors) are shown in Table **41**. Degarelix ranked 1st (SUCRA = 0.8288) followed by relugolix (SUCRA = 0.6434) and leuprolide (SUCRA = 0.0279).

Table 41**: SUCRA Ranking for MACE: Primary Analysis**

Treatment	SUCRA
Relugolix	0.6434
Degarelix	0.8288
Leuprolide	0.0279

SUCRA: surface under the cumulative ranking; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

SUCRA values for the NMA of MACE based on the sensitivity analysis excluding the Margel 2019 study (i.e., individual effects model with informed priors) are shown in Table **42** Relugolix ranked 1st (SUCRA = 0.7709) followed by degarelix (SUCRA = 0.6859) and leuprolide (SUCRA = 0.04319), suggesting that relugolix has a greater probability (77%) of being ranked first compared to other treatments.

Table 42**: SUCRA Ranking for MACE: Sensitivity Analysis Without Margel**

Treatment	SUCRA
Relugolix	0.7709
Degarelix	0.6859
Leuprolide	0.04319

SUCRA: surface under the cumulative ranking; Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W

B.2.9.3. Summary of results from published NMA (28)

In 2022, Sari Motlagh and colleagues (88) published an SLR and NMA comparing the efficacy and safety of relugolix in advanced prostate cancer.

Compared with GnRH agonists, relugolix (RR: 1.09, 95% CrI: 0.95–1.23) and degarelix (RR: 0.98, 95% CrI: 0.91–1.06) were not associated with a significantly higher likelihood of 12-month castration rate. However, based on Bayesian analysis

and analysis of the treatment ranking according to SUCRA, it was highly likely that relugolix was the top treatment to induce sustained castration. Similarly, in our primary and sensitivity analysis (in which degarelix was excluded) relugolix also ranked first according to SUCRA treatment ranking. Moreover, relugolix had a significant benefit on achieving testosterone suppression to castrate levels compared with leuprolide 22.5mg Q12W/7.5mg Q4W (OR = 2.89; 95% CI: 1.46 6.57), goserelin (OR = 2.81; 95% CI: 1.08, 12.67), and leuprolide 3.75mg Q4W (OR = 2.85; 95% CI: 1.12, 13.05).

In a subgroup analysis, two different interventions including relugolix and degarelix were conducted for CV events. Compared with GnRH agonists, they found that relugolix 0.44, 95% CrI: 0.16–1.2) and degarelix (RR: 0.74, 95% CrI: 0.37–1.52) were not associated with a lower likelihood of 12-month CV event rates. However, based on SUCRA probability ranking analysis, it was highly likely that relugolix was better than degarelix and GnRH agonists in terms of a lower likelihood of 12-month CV events. Nevertheless, the definition of CV events was different among the efficacy and safety trials and these trials did not report the various CV event results in detail.

The NMA from the company also found no statistically significant difference in terms of MACE or CV-related events between relugolix versus either of the other comparators, both in the primary analysis and sensitivity analysis (in which the Margel study was excluded). However, based on SUCRA probability ranking analysis it was highly likely that relugolix was better than degarelix and leuprolide. These results were based on a sensitivity analysis excluding the Margel study whereas in the primary analysis, degarelix ranked 1st (SUCRA = 0.8288) followed by relugolix (SUCRA = 0.6434) and leuprolide (SUCRA = 0.0279). This is likely due to differences in methodology and included trials between the two NMAs.

B.2.9.4. Uncertainties in the indirect and mixed treatment comparisons

The analysis was subject to several limitations that are common to network meta-analyses in general: heterogeneity between studies. The analysis was based on an SLR of published reports of clinical trials identified by the SLR. As such, the analysis

was not based on directly observed outcomes. In the SLR, only randomized control trials were considered and due to this, methods such as matching-adjusted indirect comparison, simulated treatment comparison, or multi-level network meta-analysis were not considered, as these require patient-level data.

In both testosterone suppression and MACE, the number of studies was small and the estimated relative treatment effects were associated with uncertainty as reflected by the wide credible intervals. For the NMA of testosterone suppression to castrate levels, only 5 studies were included, whereas the NMA of MACE included just 3 studies. Among the eligible studies, there was considerable heterogeneity in timing of castration assessment, which ranged from 1 month (28 days) to 1 year (364 days). This may have biased the results of the NMA to the extent that timing of assessment may modify the treatments effects on testosterone suppression to castrate levels.

For the MACE outcome, there was heterogeneity with respect to the types of events that were reported. Numbers of MIs and fatal CV-related events were available from all three studies. However, numbers of strokes and IHD were reported only for HERO and CS21. Information on other non-fatal CV-related events was available from the HERO and Margel 2019 study, but the types of events included as “other” differed; in HERO, these included carotid arteriosclerosis and transient ischemic attacks while in Margel 2019 they included transient ischemic attack, cerebrovascular events, heart catheterization, and cardiac-related hospitalization. These differences may have introduced bias to the NMA to the extent that different events being reported (or omitted) are likely to modify the treatment effects of MACE and CV-related events. The control arm in the Margel 2019 study was a mix of GnRH agonists, based on physician preference. For the purposes of the NMA, it was assumed that the control arm represented leuprolide. Finally, the findings contrast with published analyses of the HERO trial, in which it was demonstrated that relugolix had a significant reduction in the cumulative incidence of MACE versus leuprolide (38).

B.2.10. Adverse reactions

Adverse events (AEs) were collected from the time the first dose of study drug was administered until the follow-up visit approximately 30 days after the last dose of relugolix or 12 weeks plus 30 days after the last leuprolide injection, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurred first. Study procedure-related adverse events were collected from the signing of the informed consent form (ICF). Unless otherwise specified, all AEs described are treatment emergent.

An overall summary of AEs is presented in Table 43.

Table 43: Overview of Adverse Events (Safety Population)

No. of Patients with at Least One AE, n (%)	**Relugolix (N = 622) [a]**	**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 was 10 Dec 2019. Abbreviations: AE = adverse event; 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.

The overall incidence of adverse events was consistent across treatment groups with at least one AE reported for 578 patients (92.9%) in the relugolix group and 288 patients (93.5%) in the leuprolide group.

AEs grade ≥ 3, and AEs grade ≥ 3 related to study drug were reported with similar frequencies across the treatment groups. Serious AEs were reported at an overall lower percentage in the relugolix group (12.2%) relative to the leuprolide group (15.3%), though serious AEs related to study drug were reported at comparable low

incidence (1.0% in each treatment group). AEs with fatal outcome were reported at overall lower incidence in the relugolix group (1.1%) relative to the leuprolide group (2.9%).

AEs leading to study drug withdrawal, AEs leading to study drug interruption, AEs related to study drug, and serious AEs leading to treatment discontinuation were reported at higher incidences in the relugolix group relative to the leuprolide group. Given the differences in the route of administration between the study drugs, action taken could more often be taken directly for relugolix (daily oral route) versus leuprolide acetate (3-month depot subcutaneous). As such, depending on the individual patient schedule for leuprolide dosing relative to the onset of a given AE, interruption or withdrawal of treatment was not possible for patients in the leuprolide group, including for a fatal event. All fatal events in the leuprolide group (nine patients [2.9%]) were not captured as AEs leading to study drug discontinuation. This difference in action taken with study drug is also seen in the percentage of overall serious AEs leading to study drug discontinuation, 1.6% in the relugolix group and 0.3% in the leuprolide group.

Additionally, a total of 52 patients (35 in the relugolix group and 17 in the leuprolide group) were reported to have an AE with onset after completion of the protocol-specified safety reporting period. These AEs were all assessed as unrelated to study drug and were reported following initiation of an alternative hormonal therapy for 12 of 35 patients in the relugolix group and three of 17 patients in the leuprolide group (59); the remaining patients had events reported following completion of the safety reporting period. Five of the 35 patients in the relugolix group were reported to have serious AEs; all were assessed by the investigator as not related to study drug. In one patient, the serious AE (general physical health deterioration) was fatal. Two of the 17 patients in the leuprolide group were reported to have serious AEs; each assessed as not related to study drug.

A summary of AEs reported for at least 5% of patients (per preferred term) is presented in Table 44.

Table 44: Summary of Adverse Events reported for ≥ 5% of patients in either treatment group by preferred term (Safety Population)

Preferred Term No. of Patients with at Least One AE, n (%)	Relugolix (N = 622) [a]	Leuprolide (N = 308)
Any	578 (92.9%)	288 (93.5%)
Hot flush	338 (54.3%)	159 (51.6%)
Fatigue	134 (21.5%)	57 (18.5%)
Constipation	76 (12.2%)	30 (9.7%)
Diarrhoea	76 (12.2%)	21 (6.8%)
Arthralgia	75 (12.1%)	28 (9.1%)
Nasopharyngitis	59 (9.5%)	29 (9.4%)
Back pain	50 (8.0%)	28 (9.1%)
Hypertension	49 (7.9%)	36 (11.7%)
Weight increased	49 (7.9%)	20 (6.5%)
Insomnia	43 (6.9%)	14 (4.5%)
Pollakiuria	37 (5.9%)	20 (6.5%)
Nausea	36 (5.8%)	13 (4.2%)
Nocturia	36 (5.8%)	19 (6.2%)
Dizziness	35 (5.6%)	17 (5.5%)
Headache	35 (5.6%)	13 (4.2%)
Pain in extremity	33 (5.3%)	19 (6.2%)
Asthenia	32 (5.1%)	21 (6.8%)
Urinary incontinence	30 (4.8%)	16 (5.2%)
Hyperhidrosis	15 (2.4%)	16 (5.2%)

The database lock date was 10 Dec 2019. Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the treatment group; n=number of patients with specified AE. Patients with multiple events for a given preferred term are counted only once for each preferred term. Events are sorted by decreasing frequency of preferred term in the relugolix group. MedDRA Version 22.0.

More details on adverse events reported in the HERO trial can be found in Appendix F: Adverse reactions.

B.2.10.1. Major adverse cardiovascular events

MACE was searched for using a composite query inclusive of the Myocardial Infarction SMQ (broad) and Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ (broad), as well as deaths due to all causes. The

resulting adverse events with or without a self-reported medical history of MACE were summarized by preferred term in Table 45. These were not adjudicated.

AEs associated with MACE were reported for fewer patients in the relugolix group (18 patients [2.9%]) compared with the leuprolide group (19 patients [6.2%]).

The protocol exclusion criteria specified that patients at a substantial immediate risk of a MACE were not eligible for enrolment. Given the study's exclusion criteria, patients with a medical history of MACE comprised a smaller proportion of patients in both treatment groups (84 patients [13.5%] in the relugolix group vs 45 patients [14.6%] in the leuprolide group) (Table 45) than the reported prevalence of approximately 30% in a non-selected population of men with advanced prostate cancer (39, 89).

A post hoc exploration of the incidence of events in patients with or without a reported medical history of adverse CV events was performed. In the subgroup of patients with a reported medical history of MACE, the percentage of patients with at least one AE associated with MACE while on study drug treatment was lower in the relugolix group (3.6%) than the leuprolide group (17.8%), reflecting a 5.8-fold higher odds of having an event in men treated with leuprolide compared with relugolix (Table 45). When the incidence was adjusted for exposure to treatment, the difference between the relugolix and leuprolide groups remained: the exposure-adjusted event rate for an AE associated with MACE was 3.3 in the relugolix group and 7.0 in the leuprolide group.

The cumulative incidence of time to MACE is shown in Figure 20**,** and Kaplan-Meier estimates for time to MACE is provided in Table 46

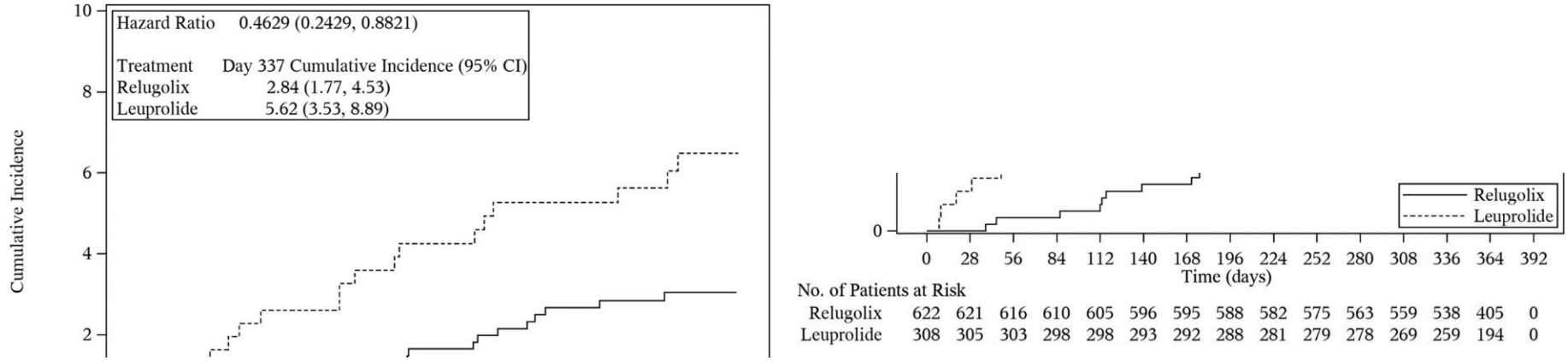
Table 45: Major Adverse Cardiovascular Events with or without a Medical History of a Major Cardiovascular Adverse Event by Preferred Term (Safety Population)

Preferred Term	Relugolix (N = 622)		Leuprolide (N = 308)	
	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
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
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

Preferred Term	Relugolix (N = 622)		Leuprolide (N = 308)	
	Patients with MACE MH (N = 84)	Patients without MACE MH (N = 538)	Patients with MACE MH (N = 45)	Patients without MACE MH (N = 263)
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%)
Multiple organ dysfunction syndrome	0	0	1 (2.2%)	0
Transient ischaemic attack	0	0	2 (4.4%)	2 (0.8%)

The database lock date was 10 Dec 2019. Abbreviations: AE = adverse event; CI = confidence interval; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; MH = medical history; N = number of patients in the treatment group; n = number of patients with specified AE; 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.

Figure 20: Cumulative Incidence of Time to Major Adverse Cardiovascular Events (Safety Population)



Abbreviations: CI = confidence interval. The database lock date was 10 Dec 2019.

Table 46: Kaplan-Meier estimates for time to major adverse cardiovascular events (Safety Population)

	Relugolix (N = 622) [a]	**Leuprolide (N = 308)**
Time to Major Adverse Cardiovascular Events in Days [a]		
No. of events (%)	18 (2.9)	19 (6.2)
No. of censored (%)	604 (97.1)	289 (93.8)
Median (95% CI) [b]	NE (NE, NE)	NE (NE, NE)
Q1, Q3	NE, NE	NE, NE
Kaplan-Meier estimates, %		
MACE rate at Day 85 (95% CI) [b]	0.32 (0.08, 1.28)	2.60 (1.31, 5.13)
MACE rate at Day 169 (95% CI) [b]	1.15 (0.55, 2.39)	3.92 (2.25, 6.80)
MACE rate at Day 253 (95% CI) [b]	2.15 (1.25, 3.68)	5.27 (3.26, 8.46)
MACE rate at Day 337 (95% CI) [b]	2.84 (1.77, 4.53)	5.62 (3.53, 8.89)
Hazard ratio to leuprolide (95% CI) [c]	0.4629 (0.2429, 0.8821)	

The database lock date was 10 Dec 2019. Abbreviations: CI = confidence interval; MACE = Major Adverse Cardiovascular Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the treatment group; NE = not estimable; Q1 = 25th percentile; Q3 = 75th percentile. [a] Time to MACE was defined as time from the date of first dose to the initial event of MACE. [b] 95% CI in each treatment group was calculated by log-log transformation of survival function in each treatment group. [c] Hazard ratio in comparison of relugolix to leuprolide was performed using Cox proportional hazard model. MedDRA Version 22.0.

The Kaplan-Meier curves for time to event separated within the first 4 weeks of the study and continued to separate through the safety-follow up visit (Figure 20). After 48 weeks of treatment, the estimates of MACE rate continued to be lower in the relugolix group at 2.84% (95% CI: 1.77%, 4.53%) compared with the leuprolide group at 5.62% (95% CI: 3.53%, 8.89%). This demonstrates a 54% reduction in risk of MACE in the relugolix group compared with leuprolide (hazard ratio = 0.4629; 95% CI: 0.2429, 0.8821) (Table 46).

More details of adverse cardiovascular events and all the components thereof can be found in Appendix F: Adverse reactions.

B.2.11. Ongoing studies

B.2.11.1. Phase 1 study (NCT04666129) evaluating relugolix in combination with abiraterone (Part 1) or apalutamide (Part 2)

This is an ongoing, 52-week, open-label, parallel cohort, safety and tolerability study of relugolix in combination with abiraterone with a corticosteroid (Part 1), or apalutamide (Part 2) (Clinical Trial Identifier NCT04666129). This study was sponsored by Myovant Sciences GmbH.

Each part of the study includes a 12-week primary study treatment period and a 40-week safety extension period. Eligible patents include those with metastatic HSPC (Part 1 and Part 2), non-metastatic castration-resistant prostate cancer (CRPC) (Part 2) or metastatic CRPC (Part1). Patients completing ≥12 weeks were included in an interim report, published in Targeted Oncology (90). An overview of the interim results (which show no change in the risk-benefit profile of relugolix when administered with abiraterone or apalutamide) is presented in Appendix M: Additional clinical evidence (M1.3).

B.2.11.2. RENAISSANCE - A multi-centre, non-interventional study of RElugolix as aNdrogen-deprivAtion therapy In patientS with advanced hormone-Sensitive prostate cANCEr

This cohort study (sponsored by Accord Healthcare) (91) will be conducted in patients who are initiating treatment with relugolix. This prospective study is designed to capture the actual experience of patients with advanced HSPC treated with relugolix by collecting data on treatment patterns, effectiveness and persistence. Patients will be followed prospectively for up to 1 year from the date of signed informed consent (enrolment). The study will enrol approximately 300 patients treated with relugolix with a primary goal to establish a database of clinical data from this patient cohort. Results are expected Q3 2026.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Summary of evaluation of response to study intervention

The pivotal phase 3 HERO study enrolled 934 patients with advanced prostate cancer who required, per the investigator's assessment, 1 year of ADT. The study included patients with PSA biochemical relapse following primary surgical treatment or radiotherapy with curative intent, newly diagnosed metastatic prostate cancer, or advanced localized disease for which immediate primary surgical treatment or RT was unlikely to be curative.

A total of 624 patients were randomized to receive relugolix and 310 patients to leuprolide. The primary endpoint was the sustained castration rate (< 50 ng/dL). Secondary endpoints were testosterone and PSA kinetics, changes in FSH, quality of life, safety, and pharmacokinetics.

Relugolix successfully met both evaluation criteria to assess the primary endpoint of achieving and maintaining sustained testosterone suppression to castrate levels through 48 weeks. The study demonstrated that 96.7% of patients who received relugolix achieved and maintained sustained testosterone suppression below castrate levels (< 50 ng/dL) from Week 5 Day 1 (Day 29) to Week 49 Day 1 (Day 337) (95% CI: 94.9%, 97.9%) with the lower bound of the 95% CI above 90% (an efficacy threshold required by FDA).

All alpha-protected secondary endpoints tested, including castration rate on Week 1 Day 4 and Week 3 Day 1, PSA response rate at Week 3 Day 1, profound castration rate at Week 3 Day 1, and FSH level at Week 25 Day 1 demonstrated statistical superiority of relugolix to leuprolide ($p < 0.0001$).

Consistent with its mechanism of action, relugolix produced a more rapid suppression of testosterone and PSA response compared with leuprolide, without testosterone surges or clinical flare. In addition, testosterone recovery was observed to be faster following

therapy discontinuation of relugolix than with discontinuation of leuprolide. This testosterone surge has been suggested to cause clinical disease flares, with reports of increased bone pain, pathologic fractures, spinal cord compression, bladder outlet obstruction (30). Not only does treatment with relugolix avoid the potential safety risks of a surge in testosterone, the rapid suppression of testosterone may also be beneficial for clinicians planning to initiate concomitant therapies, like radiation therapy, after the patient has achieved castrate levels of testosterone. Relugolix was generally well-tolerated with a tolerability profile similar to leuprolide and consistent with known effects of other GnRH agonists, but without testosterone surges and clinical flares.

Relugolix decreased the risk of MACE by 54% compared with leuprolide in a prespecified safety analysis. Of patients reporting a medical history of MACE, the odds of developing MACE during treatment in the leuprolide group was approximately 5.8 times higher than that in the relugolix group. Existing literature has similarly demonstrated that risk of MACE in patients with prostate cancer increases with the use of GnRH receptor agonists. The early cardiovascular risk associated with GnRH receptor agonist treatment in men with pre-existing cardiovascular disease was reported by Albertsen et al. (39), after conducting a large meta-analysis designed to compare the efficacy of GnRH receptor agonists against the GnRH receptor antagonist, degarelix. In the study, among men with preexisting cardiovascular disease, the risk of cardiac events within 1 year of initiation of therapy was significantly lower among men treated with a GnRH receptor antagonist compared with an GnRH receptor agonist (hazard ratio: 0.44; 95% CI: 0.26, 0.74; p = 0.0002). These findings were replicated in a randomized, open-label prospective phase 2 study comparing leuprolide with degarelix, showing a statistically significant increased risk of both cardiovascular events and major cerebrovascular events in patients treated with the receptor agonist (p = 0.013) (7).

In the C27003 study, men with intermediate-risk localized prostate cancer eligible for 6-month ADT (with baseline testosterone >150.0 ng/dL and PSA >2.0 ng/mL) and subsequent EBRT were treated with either relugolix (320 mg on day 1 and 120 mg daily thereafter; n = 65) or degarelix (240 mg on day 1 and 80 mg every 4 weeks thereafter; n = 38) for 24 weeks. The characteristics of

the 103 patients and their baseline data, as well as the details of RT, were similar between the relugolix and degarelix groups. The castration rates for the threshold of 50 ng/mL or 20 ng/dL were 95% or 82% with relugolix (median: 4 days) and 89% or 68% with degarelix (median: 3 days), respectively. In both groups (relugolix 26%, degarelix 29%), the prostate volume was reduced from baseline after 8–12 weeks of treatment. Similarly, at 24 weeks, ≥50% PSA reduction (relugolix 98%, degarelix 100%) and ≥90% PSA reduction (relugolix 95%, degarelix 92%) were detected in most of the patients. By 12 weeks after the discontinuation of treatment, recovery of testosterone levels to baseline or 280 ng/mL occurred in 52% of the relugolix patients vs 16% of the degarelix patients. In addition, changes in the QoL scores during 24-week treatment, as well as sexual activity or ADT-related symptoms, were similar between the two arms. Most of the patients (relugolix 86%, degarelix 97%) had at least one AE, while severe (grade ≥3) events were rare (relugolix 2%, degarelix 11%) and none discontinued treatment due to side effects. These data indicated the comparable efficacy of relugolix and degarelix in achieving androgen/PSA reduction in men with prostate cancer.

In conclusion, relugolix can potentially provide a therapeutic option with an improved benefit: risk profile compared with the GnRH receptor agonists, the current standard of care ADT. The safety and efficacy data from the pivotal phase 3 study demonstrates the ability of relugolix to provide comparable or superior efficacy to leuprolide, while providing a substantial reduction in serious, and possibly fatal, adverse CV events. In addition, the phase 2 study comparing relugolix with degarelix indicated comparable efficacy in achieving androgen/PSA reduction in men with prostate cancer, with an improved testosterone recovery in relugolix patients.

B.2.12.2. Strengths and limitations of the clinical evidence base for relugolix

Relugolix presents a valuable treatment option for men with advanced prostate cancer where ADT is indicated. In the pivotal phase 3 trial HERO, relugolix successfully met both evaluation criteria to assess the primary endpoint of achieving and maintaining sustained testosterone suppression to castrate levels through 48 weeks. All alpha-protected secondary endpoints tested demonstrated statistical superiority of relugolix to leuprolide and the odds of developing MACE during treatment in the leuprolide

group was approximately 5.8 times higher than that in the relugolix group. Relugolix provides rapid testosterone suppression (with no initial surge in testosterone upon treatment initiation) combined with the benefits of oral administration and improved cardiac safety over leuprolide.

A potential limitation of the study was the choice of comparator. Degarelix, with an identical model of action, may have been more appropriate. However, in England degarelix is restricted to men with spinal metastases. Another limitation is the lack of evidence on survival or disease progression and whilst relugolix may reduce the risk of MACE, this was not formally tested. The lack of blinding could have influenced investigators' assessments of safety and patients' responses on QoL questionnaires, and despite the high compliance reported for relugolix administration in this study, this may not reflect compliance and adherence in a real-world setting. In addition, there is concern about the potential for reduced treatment adherence with an oral ADT agent and the negative effects that it could have on patient outcomes. NCCN guidelines suggest that ongoing monitoring of testosterone levels may be useful to confirm sustained testosterone suppression to castrate levels (92). However, as stated previously, a recent patient preference survey (sponsored by Accord Healthcare) suggests that oral administration is seen as a benefit by patients (50).

As prostate cancer progresses, ADT is commonly co-prescribed in combination with complementary agents that suppress extra testicular testosterone, such as enzalutamide or abiraterone. Thus far, there is limited data on the efficacy and safety of relugolix in combination with these agents. Sub-group analysis of patients from the HERO study that received combination treatment with either enzalutamide or docetaxel showed no new safety concerns. Interim results from the Apa RP study (see section 0) in which 12 patients received relugolix and apalutamide for 28 days demonstrated that relugolix administered at approved standard doses concurrently with apalutamide was effective in maintaining castrate testosterone levels in high-risk localised prostate cancer without new safety signals (93). Real world evidence data from two studies in the United States, showed no new safety signals with relugolix in combination either ARIs or docetaxel (90, 94).

In the C27003 study, both degarelix and relugolix showed similar efficacy (the study was not designed or powered to make formal statistical comparisons between relugolix and degarelix). Both drugs rapidly induced and maintained castration during the treatment period. The rate of gonadotrophin and testosterone recovery after treatment discontinuation was rapid with relugolix which was associated with a rapid improvement in a range of castration-related symptoms on QoL measures. The most important aspect of relugolix over degarelix is that patients avoid the injection site reactions related with degarelix. Relugolix also provides a more flexible dosing profile and is ideal for prompt cessation because of adverse events or intolerance. This is particularly beneficial for men undergoing short-term ADT in combination with RT. However, a limitation of this study is that most of the participants had intermediate-risk prostate cancer which is not within the licensed indication for relugolix.

The lack of blinding in this study is also a potential limitation. Although knowledge of treatment assignments is unlikely to have had a meaningful impact on testosterone levels or other pharmacodynamic endpoints, as with the HERO trial, it could have influenced investigators' assessments of safety and patients' responses on QoL questionnaires. Despite the high compliance reported for relugolix administration (>98%), another potential limitation of this study is that it may not reflect compliance and adherence in a real-world setting. Inconsistent dosing carries the danger of ineffective therapeutic delivery and suboptimal treatment outcomes. Although compliance is more difficult to monitor with self-administered oral medications compared with injections administered by healthcare professionals, compliance can be monitored indirectly with testosterone or PSA levels.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

An SLR was conducted to identify published economic models, available economic evidence including economic evaluations, costs and resource use, as well as any relevant utility data for patients with hormone sensitive prostate cancer. A detailed description of the SLR is provided in Appendix G: Published cost-effectiveness studies.

B.3.2. Economic analysis

A *de novo* economic model was developed as currently there is no published UK cost effectiveness analysis which compares relugolix with GnRH agonists or degarelix.

B.3.2.1. Patient population

The cost-effectiveness of relugolix was evaluated in patients with advanced HSPC, including those with the following disease states: those with locally advanced (LA) disease who are not candidates for curative therapy, those with biochemical relapse (BR) following local therapy with curative intent and without metastatic disease, and those with metastatic disease (including patients with BR and evidence of metastatic hormone-sensitive prostate cancer; mHSPC). The analysis reported in this submission does not assess the cost-effectiveness of relugolix in the high-risk localized setting, as this was subject to an ongoing license variation application at the time of dossier preparation (now confirmed approved by the MHRA). Furthermore, as high-risk localized patients comprised only a small subset of the HERO study, there would be insufficient data to populate this subgroup.

Given that one of the important benefits of relugolix is a reduced risk of MACE when compared with GnRH agonists (see section B.2.9), the population is further stratified into patients with and without a history of MACE. With respect to this outcome, the only difference between the advanced HSPC population considered by the model and the subpopulation of high-risk localised prostate cancer patients is duration of treatment. Treatment in the adjuvant and neoadjuvant setting is for a fixed duration, whereas treatment may be continued post-progression in advanced HSPC.

In summary, we anticipate the cost-effectiveness of relugolix in advanced HSPC to be generalisable to the high-risk localized setting that has recently been added to the MHRA licence.

As discussed in B.1.1, degarelix is only recommended by NICE in the subpopulation of patients with spinal metastases, therefore we include a subgroup analysis (see section B.3.11) in which we generate cost-effectiveness results against both GnRH

agonist and degarelix in the metastatic HSPC (mHSPC) subgroup (32% of the total model cohort). In the absence of a formal analysis in patients with spinal metastases, this broader metastatic subgroup is considered the best proxy for patients with spinal metastases.

Baseline characteristics for the model cohort are presented in Table 48. Mean age was assumed to be the same as the HERO trial (38). The initial proportion of patients in the LA state was based on the proportion of patients enrolled in HERO and classified as LA (38). For the BR state, the initial proportion was based on the proportion of patients enrolled in HERO classified as BR and without distant metastases at baseline; the initial proportion in mHSPC was based on patients enrolled in HERO with presence of distant metastases at baseline.

Because the HERO trial excluded patients with a MACE in the prior 6 months, and therefore may not be representative of the population who would be expected to receive treatment with relugolix in clinical practice, the initial proportion with history of MACE was assumed to be 30.4% for the combined population based on a study by Albertsen et al (39), that utilised data from 6 randomised trials of GnRH antagonists versus LHRH agonists (39). To account for impacts that age may have on history of MACE, an adjustment factor of 1.241 was applied to the initial proportion of patients with history of MACE (30.4%) representing the ratio of patients with a MACE in a 12-month lookback period by age group relative to all patients. This estimate was based on analyses of a claims dataset (n = 43,224; data on file). Mean body surface area (BSA) and mean weight (kg), required for calculating dosages for IV medications were based on data from the HERO trial (data on file).

Table 48: Characteristics of the model cohort

Characteristic	Parameter Value	Source
Mean age (years)	71	Data on file
Initial health state probabilities		
LA	27.0%	Shore, 2020 (38)
BR, non-metastatic	41.0%	Shore, 2020 (38)
Metastatic	32.0%	Shore, 2020 (38)
History of MACE	37.7%	HERO trial. Data on file

Body surface area (m2)	1.97	Derived from mean weight and height (data on file) using Mosteller formula* (97)
Weight (kg)	81.06	HERO trial. Data on file

Other than the proportion of the population with a history of MACE, the model population therefore corresponds to the population evaluated in the HERO trial (which also comprises a small proportion of high-risk localised patients included within the recent marketing authorization extension, see Section B.1.1.

B.3.2.2. Model structure

A Markov Cohort Model (MCM) programmed in Microsoft Excel® was employed to evaluate the cost-effectiveness of relugolix in advanced HSPC. An MCM approach was used for several reasons including the relatively long time-horizon required to capture the effects of treatment on outcomes and costs, the relatively complex set of interrelated health states that represent the natural history and treatment of advanced HSPC, the short follow-up of the HERO trial relative to the modelling time horizon, and the need to estimate long-term outcomes for subsequent health states (i.e., those that patient transit to following treatment initiation) (98). While partitioned survival models are frequently used in economic evaluations of oncology therapies (99), data on overall survival (OS) and progression free survival (PFS) from the HERO trial were not sufficiently mature to support the use of such an approach.

A simplified schematic of the model structure is shown in Figure 21. Model states were defined according to:

1. Clinical presentation at baseline (i.e., LA, BR, and metastatic hormone-sensitive prostate cancer [mHSPC]);

2. Whether patients were on- or off-treatment;

3. Levels of serum testosterone (i.e., above or below castration levels);

4. Sensitivity and resistant to hormone therapy; and

5. Vital status (i.e., alive or dead).

The model was further comprised of two sub-models for patients with prior MACE and those with no prior MACE (note: The Prior MACE and No Prior MACE sub-models are not depicted explicitly in Figure 21 as the health states in each sub-model are identical).

Each sub-model included the following ten health states:

1. LA On-Treatment Not Castrated;
2. LA On-Treatment Castrated;
3. LA Off-Treatment;
4. BR On-Treatment Not Castrated;
5. BR On-Treatment Castrated;
6. BR Off-Treatment;
7. mHSPC Not Castrated;
8. mHSPC Castrated;
9. Non-metastatic castration-resistant prostate cancer (nmCRPC);
10. Metastatic castration-resistant prostate cancer (mCRPC).

Patients without history of MACE enter the No Prior MACE sub-model, while those with a history of MACE enter the Prior MACE sub-model. Patients in the No Prior MACE sub-model transit to the Prior MACE sub-model upon experiencing a first MACE. Patients in the Prior MACE sub-model were assumed to be at increased risk of subsequent MACE compared to those in the No Prior MACE sub-model. In either sub-model, patients start in one of the LA Not Castrated On-treatment, BR Not Castrated On-treatment, or mHSPC Not Castrated states. The initial probabilities starting in each sub-model and health state were based on disease characteristics for patients enrolled in HERO. These have been provided above in Table 48.

LA, BR, and mHSPC patients on ADT may achieve sustained castration levels of testosterone, experience PSA progression, develop distant metastases (if in the LA or BR states) or die. Those achieving sustained castration transit to the LA Castrated On-treatment, BR Castrated On-treatment, or mHSPC Castrated On-treatment states, as appropriate, three months after initiation of therapy. Patients without

sustained castration stay in the same state and may be at increased risk of PSA progression. A proportion of patients in the LA and BR Castrated On-treatment states may discontinue ADT (including potentially intermittent therapy) and transit to corresponding Off-treatment states.

Patients in the LA On-treatment or BR On-treatment states who experience PSA progression are subsequently classified as castration-resistant and transit to the non-metastatic castration resistant prostate cancer (nmCRPC) state regardless of whether they had sustained castration. Patients in either of the LA or BR Off-treatment states with PSA progression are assumed to remain hormone-sensitive and initiate ADT again; as such, they transit to the BR On-treatment Not Castrated state.

Patients in the LA and BR states who develop distant metastases transit to the mHSPC state. Patients in mHSPC with PSA progression are assumed to be castration-resistant and transit to the metastatic castration resistant prostate cancer (mCRPC) state. Patients are assumed to remain on ADT whilst they have mHSPC. However, ADT may be continued once the patient has transitioned to the mCRPC state, consistent with the prescribing information provided in the SmPC for leuprolide, degarelix and triptorelin (42, 100-102).

Patients in nmCRPC are at risk of developing distant metastases and death. Those developing distant metastases transit to the mCRPC state. Patients in the nmCRPC and mCRPC states remain on ADT indefinitely (i.e., no intermittent therapy) and add treatment with androgen receptor inhibitors (ARIs) or chemotherapy. Subsequent lines of therapy for mCRPC patients were not modelled explicitly with additional health states, but the model allows for the possibility that patients may get up to three additional lines after entering mCRPC.

All patients are at risk of MACE, which may or may not be fatal. Risk of MACE differed by treatment and for patients who are on or off-therapy; patients who discontinue ADT were assumed to have a reduced risk of MACE after a period of time, post-discontinuation. MACE was assumed to include non-fatal MI, non-fatal stroke, non-fatal transient ischemic attack (TIA), and any fatal CV-related events.

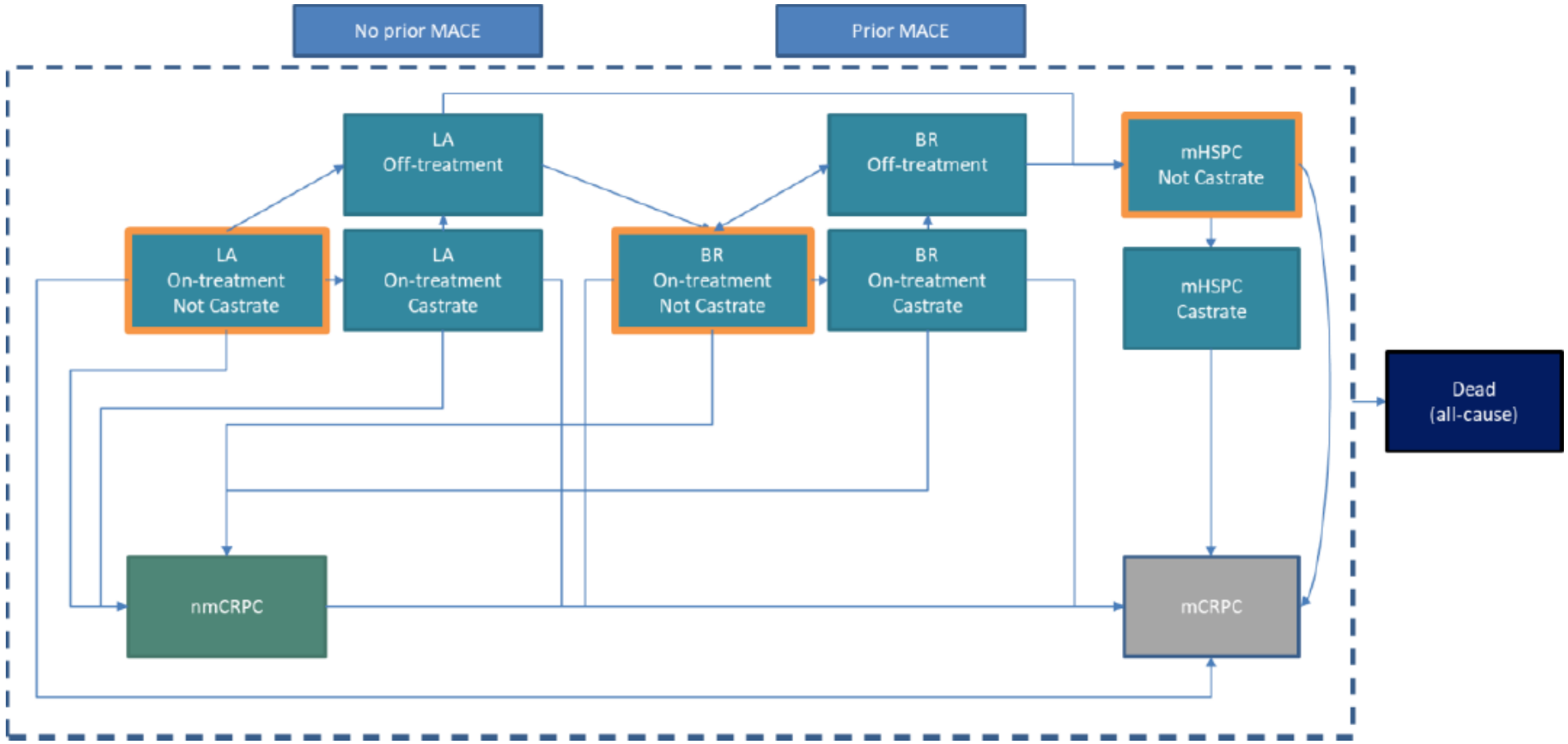
Patients in all states were at risk of death from causes other than MACE or prostate cancer (PC). Patients in metastatic states were also at risk of death from PC.

The analysis was conducted from the perspective of the NHS in line with current NICE guidelines (103). The base-case analysis thus considers all costs incurred within the health care sector. Costs and outcomes are discounted at an annual rate of 3.5%, in line with the NICE reference case (103). As such, only direct healthcare costs associated with advanced HSPC and its management were considered and the model does not consider societal costs.

All outcomes were evaluated over a lifetime time horizon consistent with recommended good practices for cost-effectiveness analysis (104-106). The model has the flexibility to use alternative time horizons up to a maximum of 40 years (this would permit consideration of a population with a mean starting age of 60 years and following patients until age 100 years, when virtually all would be projected to be dead). Under the assumption that the average starting age for the patient population in the primary analysis is 71 years, a 26-year time horizon was employed in the base case.

The model employed a periodicity (i.e., model cycle length) of three months (i.e., quarterly). Although a monthly periodicity was considered, it was determined that a monthly cycle length would make model calculations intractable.

Figure 21: Simplified Schematic of Markov Model Structure



LA= locally advanced. BR= biochemically recurrent. m= metastatic. nm= non-metastatic. HSPC= hormone-sensitive prostate cancer. CRPC= castration-resistant prostate cancer

Notes: The states outline in orange are the states that patients can start in; The Prior MACE and No Prior MACE sub-models are not depicted explicitly, as the health states in each sub-model are identical.

Model parameters were estimated using data from the HERO trial as well as published sources. Published sources were identified from SLRs and targeted literature searches, as well as from prior economic evaluations by the Institute for Clinical and Economic Review and NICE (see Section B.3.1). In the sections below, methods for model estimation for specific model parameters are described.

The principal driver of value in the model is the decrease in the rate of MACE based on the treatment effect from HERO (for GnRH agonists) or the ITC (for degarelix) (see section B.2.9). A differential effect on progression-free survival of advanced prostate cancer between relugolix and its comparators is not assumed and therefore the model structure serves purely as a basis for modelling time on treatment for the different comparators, effect on MACE, and patient health-related quality of life (HRQoL).

Table 49: Features of the economic analysis

	Previous evaluations	Current evaluation	
Factor	**TA404**	**Chosen values**	**Justification**
PSA Progression	A PSA progression benefit for degarelix compared with LHRH agonists was considered highly uncertain. Company's assumption of differential PSA progression for degarelix compared with LHRH agonists was therefore considered not proven	Time to PSA progression for non-metastatic patients (i.e., LA and BR) was analysed using patient-level data from HERO with stratification by clinical disease presentation at baseline and by randomised treatment arm using the Kaplan-Meier method. No differences were observed across treatment arms for PSA progression within subgroups for LA and BR.	Time to PSA progression for patients with distant metastases at baseline in HERO was analysed and stratified by treatment arm using the Kaplan-Meier method. No differences were observed across treatment arms for time to PSA progression in this subgroup.
Link between PSA progression on first-line treatment and increased risk of mortality for people with metastatic disease	No overall survival benefit for degarelix compared with LHRH agonists should have been assumed in the model	As no difference in PSA progression is assumed between relugolix and comparator, no change in prostate cancer-related death is assumed in the model.	Probabilities of death conditioned on PSA and metastatic progression were derived from clinical trials of mHSPC and mCRPC patients identified from sources employed in published economic evaluations of treatments for prostate cancer and targeted reviews of the literature
Treatment effects for fractures, joint-related signs and symptoms, and cardiovascular events	Considerable uncertainty around the estimated differences in the rates of fractures and cardiovascular events for degarelix compared with LHRH agonists. Appropriate to assume no differences for the rate of cardiovascular events and fractures between degarelix and LHRH agonists in the model	In the proposed company model, all patients are at risk of MACE, which may or may not be fatal. Risk of MACE differs by treatment and for patients who are on or off-therapy; risk of MACE is derived from an ITC. Patients who discontinue ADT are assumed to have their risk of MACE reduced after a period of time post-	An effect on MACE of GnRH antagonists vs. agonists was observed in HERO and is described expansively in the published literature (Section B.2.6.1.8).

	Previous evaluations	Current evaluation	
Factor	**TA404**	**Chosen values**	**Justification**
		discontinuation. MACE was assumed to include non-fatal MI, non-fatal stroke, non-fatal transient ischemic attack (TIA), and any fatal cardiovascular (CV)-related events.	
Time horizon	30 years	Life-time Horizon	NICE reference case (107) and given the model assumes that the average starting age of those with advanced HSPC is 71 years, a 26-year time horizon was employed in the base case. This would allow patients to be followed until 100 years, when majority of the patients would have died.
Treatment waning effect	The manufacturer applied the 1-year treatment effect observed in CS21 (76) to the parametric curves, assuming proportional hazards.	No effect on prostate cancer-specific outcomes is assumed. Effect on MACE is not assumed to wane over time.	No evidence exists that effect on MACE changes over time.
Source of utilities	Utility values in the model were obtained from health-related quality-of-life data from CS21 (76) and studies identified in the literature review. The manufacturer applied different mapping algorithms (the algorithm from the Health Economics Research Centre based on Gray et al. [2004] (108), and the algorithms from Kontodimopoulos et al. [2009] (109) and from McKenzie and van der Pol [2009]) (110) to transform health-related quality-of-life data from CS21 into utility values based on the EQ-5D questionnaire. Utility decrements associated with spinal cord compression were based on Lu et al. (111)	Utility values in the model were obtained from HERO trial data (38) (on file), which were in line with the requirements of the NICE reference case for health technology assessment (HTA) submission. For sensitivity analysis, values from the literature were sourced as part of a SLR (Section: Appendix H). Disutility data for adverse events were sourced from various Technology appraisals (TA404, TA712). These were excluded in the scenario analyses (96, 112).	NICE reference case (107).

	Previous evaluations	Current evaluation	
Factor	**TA404**	**Chosen values**	**Justification**
Duration of hormonal therapy	Assumption of hormonal therapy continuing until death in line with clinical practice	Patients with Metastatic Castration-Resistant Prostate Cancer are assumed to continue receiving ADT indefinitely, i.e., until death.	In line with clinical practice and replicated in the NICE Technology appraisal (TA404) (26)
Source of costs	British National Formulary (BNF) (113)], NHS Reference costs 2020/21 (114), PSSRU 2022 (115), KOL (key opinion leader)/ Expert opinion	British National Formulary (BNF) (113), eMIT (Drugs and pharmaceutical electronic market information tool) (116), NHS Reference costs 2021/22 (114), PSSRU 2022 (115), KOL (key opinion leader)/ expert opinion, SPC (Electronic Medicines Compendium 2021), NICE TA's.	NICE reference case (107)

B.3.2.3. Intervention technology and comparators

The intervention of interest is relugolix administered orally via loading dose of 360mg on day 1 followed by 120mg daily thereafter. This corresponds to the treatment arm in the HERO trial and the dosage in the prescribing information for relugolix provided by the EMA.

Comparators in the model are based on ADT options in the scope for which estimates of relative efficacy versus relugolix could be obtained (25). Although there are multiple GnRH agonists licensed in the UK, we consider all agonists to be of equal efficacy and safety in the model, based on the results of the ITC in section B.2.9, as well as clinical opinion (also stated explicitly within the committee's discussion of degarelix in TA404). For simplicity, we therefore present results for a blended comparator of 3-monthly leuprolide, goserelin and triptorelin based on their market shares in English prescription costs analysis (see section B.3.5.1.1) (117). The only 6-monthly formulation licensed in the UK is triptorelin 22.5mg, but Accord market research on sales of the different GnRH agonists in the UK have shown the share of triptorelin 24-weekly to be approximately 4.9%. We therefore do not consider this presentation to be relevant to the scope as it is not a material comparator within UK clinical practice. Furthermore, there are likely patient-specific factors that determine the choice of a 6-monthly injection vs. the more common 3-monthly injections, meaning that this treatment is unlikely to be displaced by a daily oral formulation.

As discussed in B.1.1, degarelix is only recommended by NICE in the subpopulation of patients with spinal metastases, as the absence of testosterone flare was considered a clinical advantage in this subgroup of patients. In section B.2.9, we demonstrated that relugolix was as effective as degarelix for prostate-specific outcomes and MACE. Furthermore, absence of testosterone flare is an attribute of both products. We consider it unnecessary to present a separate cost-effectiveness analysis against degarelix in the subpopulation of patients with spinal metastases as this would require a separate analysis considering the effects on MACE in a very narrow subpopulation. Results against degarelix are therefore only presented in the metastatic HSPC population within section B.3.11.

In the broader HSPC population (base case), degarelix is not a relevant comparator, therefore the head-to-head results of HERO inform estimates of relative effectiveness between relugolix and the blended GnRH comparator, on the basis that all GnRH analogue formulations have equivalent efficacy.

In the mHSPC subgroup analysis (a proxy for patients with spinal metastasis), relative efficacy was estimated based on an SLR of treatments for advanced HSPC, including the following therapies used as medical ADT (i.e., as opposed to surgical) for the population of interest, as described in section B.2.9:

1. Leuprolide,

2. Triptorelin,

3. Goserelin,

4. Degarelix.

B.3.3. Clinical parameters and variables

Indirect treatment comparisons (ITCs) were conducted for efficacy outcomes of different medical (i.e., as opposed to surgical) ADTs for HSPC in the population of interest (see section B.2.9). In line with clinical opinion expressed during the NICE degarelix appraisal, there was no statistically significant difference between the efficacy of different GnRHs and goserelin and triptorelin can be considered clinically equivalent to leuprolide. As stated previously, an ITC is therefore not required to inform parameters against the blended GnRH agonist and we rely on the head-to-head results from HERO in the base case analysis.

Degarelix is not a relevant comparator within the broader scope of advanced HSPC as it is only recommended in the narrow subgroup of patients with spinal metastases. However, as explained in section B.3.2.3, an analysis within that subgroup has not been conducted and we rely on cost-effectiveness vs. degarelix within the mHSPC population to draw inferences for the subpopulation with spinal metastases. In the subgroup of patients with spinal metastases, we use the results

from the ITC to populate outcomes for both leuprolide and degarelix (see Table 28 and Table 37) and only present results in the subpopulation of mHSPC patients.

Efficacy outcomes from HERO (in the broader population) or the ITCs (in the spinal metastases subgroup) corresponded to transition probabilities required to populate the economic model, including:

1. Sustained castration rate (probability of achieving castration);

2. Time to PSA progression; and

3. Incidence of MACE.

While there was a statistically significant difference in sustained castration rate in the HERO study, time to PSA progression was not found to differ significantly between relugolix and GnRH agonist. Therefore, although probability of achieving castration is implemented in the model, because there is no impact on PSA progression it has no impact on the incremental cost effectiveness ratio (ICER). Thus, as stated previously, the only clinical advantage captured for relugolix vs. the GnRH agonists (or degarelix) in the model is the effect on MACE. Other than MACE, the parameters described in Appendix O: Clinical parameters and variables, serve purely to extrapolate progression and survival and to capture the HRQoL of those patients who die from MACE.

Details of clinical parameters and variables used in the model are provided in Appendix O: Clinical parameters and variables, in subsections O1.1 Probabilities of Achieving Castration to O1.12 Probabilities of Non-MACE Adverse Events.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

Utilities were estimated by health state (i.e., pre- versus post-PSA progression and non-metastatic versus metastatic disease) based on analyses of HERO trial data (data on file). Utility values were adjusted for age-related declines in HRQoL, further details of methods are provided in Appendix P: Measurement and Valuation of health effects, in the subsection P1.1 Health-related quality-of-life data from clinical trials.

B.3.4.2. Mapping

As EQ-5D utility values were available from the HERO clinical study, no mapping was required, other than cross-walking of the 5L to the 3L instrument to permit use of the appropriate value set.

B.3.4.3. Health-related quality-of-life studies

An SLR was conducted to identify sources of HRQoL data in advanced HSPC. A detailed explanation of this is provided in Appendix H: Health-related quality-of-life studies

B.3.4.4. Health State Utilities Sourced from the Literature

The SLR conducted to identify sources of HRQOL data for those with advanced HSPC resulted in no studies being identified other than the technology appraisal of Degarelix (TA404) (96). The health state utilities used in the technology appraisal do not align with the health states used in the current model. The technology appraisal submission uses utility data based on treatment whereas the current model uses utilities based on disease progression. As a result, no literature-based scenario analysis was conducted for health state utilities in the model.

B.3.4.5. General Population Utility Values

Age- and gender-matched general population utilities were used to adjust utility values for age-related declines in HRQoL. These age-related utility adjustments were based on published UK population norms for the EQ-5D-3L as reported by Kind and colleagues. who report unadjusted mean EQ-5D index scores by age based on a nationally representative sample (118), as shown in Table 50. EQ-5D-3L values

were used over EQ-5D-5L values as per the NICE Methods Guide (119). Age-specific declines in utility were applied in the model subtracting the difference in utility for current age versus the age at entry into the model from the state- and comparator/treatment-specific utilities.

Table 50: General Population Utility Values, by Age Group

Age Group	Male Utility Value	Source
45-54	0.840	Kind, 1999 (118)
55-64	0.780	
65-74	0.780	
>75	0.750	

B.3.4.6. Adverse reactions

Although HRQoL was collected in the HERO study, we assume that the disutility of acute (i.e. temporary) adverse events would not be captured within the core prostate cancer health state values (as the EQ-5D asks about your health 'today' and was not administered regularly). The disutility of adverse events (including MACE) is therefore subtracted from the core health state values in the base case. These are excluded in a scenario analysis (Section B.3.10.3).

B.3.4.7. Utility Decrements for MACE and AEs

A chronic disutility of -0.09 for non-fatal MACE based on data from TA404 (96) was applied to the prior MACE states based on the distribution of MACE. Estimates of the disutilities associated with non-MACE grade 3-4 AEs, and their duration, is based on data from TA712 (Table 51) (112, 120) and data from a population of Type II diabetes who experience injection site reactions due to subcutaneous route of treatment administration which is used as a proxy for the modelled population (121) These values had previously been assessed by NICE and an assessment group. The estimates of the AE disutilities were applied in the base case given the frequency of administration in the trial and one-day recall period of the EQ-5D would have precluded the capture of disutility of AEs.

Table 51: Adverse Event Disutility and Duration

Health State	Disutility	Duration (Days)	Source	Justification
Hot flush	Assumed to be zero	10.5	(97, 122)	These are the values seen in the Enzalutamide NICE STA (mHSPC) [TA712 (112)]. These values will have previously been assessed by NICE and an assessment group.
Fatigue	-0.131	91.25	(123-125) (National Institute for Health and Care Excellence 2016, National Institute for Health and Care Excellence 2021)	
Arthralgia	-0.069	10.5	(126)(National Institute for Health and Care Excellence 2016, National Institute for Health and Care Excellence 2021)	
Hypertension	-0.153	10.5	(125) (National Institute for Health and Care Excellence 2016, National Institute for Health and Care Excellence 2021)	
Injection site reaction	-0.011	5	(121)	Injection site reaction value is taken from a type II diabetes population which is used as a proxy for HSPC patients.

B.3.4.8. Health-related quality-of-life data used in the cost-effectiveness analysis

The NICE methods guide (119) states that the preferred source of utility values should come from clinical studies, therefore the utility values mapped from the HERO (38) EQ-5D-5L responses as described previously (Section B.3.4) were applied in the model as the base case, as shown in Table 142 (P1.2 Health-related quality-of-life data used in the cost-effectiveness analysis). Methods of elicitation, valuation, collection time points are described in Section B.3.4.1.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify any UK healthcare resource utilities (HRU) and costs in advanced HSPC. This is detailed in Appendix I: Cost and healthcare resource identification, measurement and valuation. The HRU studies identified did not provide any information on relevant HRU values which could be utilised in the model. A series of technical appraisal reports (TA580, TA712, TA377) were utilised for the various non metastatic and metastatic health states. These are covered in more detail in Section B.3.5.2 (Health-state unit costs and resource use) These values were selected as they were relevant to the health states modelled.

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Medication Costs

Medication costs were estimated by time since entry into the state by combining estimates of the probability of being on therapy by time since therapy initiation with estimates of costs for those patients remaining on therapy.

Costs of medications per cycle were calculated by multiplying expected days of medication received per cycle by the expected cost of medication per day of use. For any given model cycle, the expected days of use of medication for each treatment strategy were based on the corresponding dosage schedule (e.g., relugolix is administered daily).

Medication costs per day of use were calculated by multiplying the costs per unit (e.g., mg) by the number of units used per day. Costs per unit were obtained by dividing the list price per pack/vial by the number of mg/ug per pack. For therapies dosed based on body surface area (BSA) or weight, the planned dose per day of use was estimated by multiplying the prescribed dose strength per meter-squared (e.g., m2) of BSA or per kg of body weight by the estimated mean BSA or mean body weight for men reported by the HERO trial (38), as appropriate. These included Docetaxel, Radium-223 and Cabazitaxel (Jevtana).

B.3.5.1.2. Dosages

The assumed dosages for each treatment regimen were based on prescribing information (Table 143: Medication Dosages; Appendix Q: Cost and healthcare resource use identification, measurement and valuation). Although we only report cost-effectiveness results for a blended GnRH comparator, dosing recommendations for the 3-monthly goserelin and triptorelin are reported for comparison purposes.

B.3.5.1.3. Percent of Patients Receiving Different Formulations of Each Drug

It is assumed that 100% of patients on relugolix receive the loading dose (360mg for one day) and subsequent maintenance doses (120mg daily).

For the blended GnRH agonist comparator it is assumed that 33%, 47% and 20% of patients are on goserelin, leuprorelin and triptorelin, respectively, based on prescription cost analysis (117). It was assumed that bicalutamide was prescribed alongside leuprolide for 100% of patients during a period of 3 weeks, in line with local NHS guidelines(127, 128). While the model has the functionality for apalutamide, enzalutamide and abiraterone with prednisolone to be prescribed alongside all treatments, for the base case it was assumed no patients received these concomitant therapies.

In the subgroup analysis, it is assumed that 100% of patients on degarelix receive the loading dose (240mg) and subsequent maintenance doses (80mg every 28 days).

B.3.5.1.4. Unit Costs of Medications

For generic medicines delivered in hospital, unit costs of medications were based on the ‘drugs and pharmaceutical electronic market information tool’ (eMIT). If the BNF price was not available, the NHS Indicative Price, sourced from the British National Formulary (BNF), was used. If the unit costs could not be found in either of these sources, then NICE technology appraisals (TAs) were used.

In the base case, the cost of a blend of GnRH agonists is used as the comparator unit cost, as explained in Section B.3.5.1.3, which costs £225.11 per 3-monthly dose. This was calculated as the weighted average cost of leuprolide (47%), goserelin (33%) and triptorelin (20%). Note that for leuprolide, the cost of Prostap (£225.72) was used in the blended comparator. Although a cheaper formulation of leuprolide (Staladex) is available, prescription cost analysis shows that this formulation only comprises 0.36% of all leuprolide 3-monthly prescriptions (117). To avoid having to create a separate comparator In the Excel model, this blended unit cost is applied to the triptorelin (3- monthly) comparator, which had the lowest share of prescriptions in

the English prescription cost analysis. It should be noted that GnRH agonist prescriptions, while initiated in hospital, are primarily delivered in the community and thus are subject to retail pharmacy pricing at an unknown level of discount.

In the base case, it is assumed that patients in nmCRPC continue receiving the same type of ADT as in HSPC. The model also has the facility to assume that patients in CRPC would instead receive a mix of different types of ADT. If this option is selected, the model cycle cost of ADT in CRPC is assumed to be £197.43 based on a simple average of the cycle cost of ADTs calculated in the model.

In the base case, patients in HSPC who fail to achieve castration are assumed to switch to a different type of ADT, which is assumed to be comprised of the same mix of ADTs described above for CRPC. Costs of subsequent treatment is discussed in section B.3.5.1.8 (Costs of Subsequent Treatments).
A summary of costs for the medications is given in Table 144, (Appendix Q: Cost and healthcare resource use identification, measurement and valuation.).

B.3.5.1.5. Costs of Administration/Dispensing of Medications

Costs of dispensing for oral medications are likely to be immaterial and therefore were assumed to be zero, though the model has the facility to consider such costs. Costs of intramuscular administration of leuprolide and other GnRH agonists was based on a split of 87% and 13% between GP practice nurse and outpatient non consultant led Urology service appointment administration respectively. This is based on IQVIA dispensing data for agonist and antagonist injections dispensed in primary care and hospital respectively (129).

Administration was assumed to require a 15-minute GP practice nurse appointment (validated by a GP practice nurse and used in Degarelix technology appraisal (TA404) (26). Administration costs in secondary care are based on outpatient clinic costs described in the 2023-25 NHS Payment Scheme, 2023/24 prices workbook (130) (Non consultant led outpatient attendance urology service: WF01A, Follow-up attendance - single professional). The estimated cost per administration is represented as a weighted average of the split between primary and secondary care administration and results in an average cost of £25.28 per administration.

Note that administration costs exclude the cost of syringes for 3-monthly triptorelin, which is only available as powder and solvent for injection in vials. Intravenous (IV) administration for other treatment options was costed at £362.00 per administration, based on SB12Z (Deliver simple parenteral chemotherapy at first attendance).

B.3.5.1.6. Drug Wastage

Drug wastage for IV therapies was calculated by rounding up the dosage in mg estimated for the mean weight or BSA to the next increment of mg per vial (e.g., for a drug with a 100 mg vial, a mean dose of 90 mg is rounded to 1 vial). Since costs of medication acquisition were applied at the beginning each model cycle, the model accounts for wastage for oral and intramuscular medications for patients who discontinue treatment in the middle of a cycle.

B.3.5.1.7. Costs of Antiandrogen Treatments During Initial ADT

For patients receiving leuprolide as initial ADT, costs of antiandrogen therapy (e.g., bicalutamide) were considered for testosterone flare. It was assumed that bicalutamide was prescribed alongside leuprolide for 100% of patients during a period of 3 weeks, in line with local NHS guidelines. Note that as bicalutamide only costs 7 pence a tablet, the model is not at all sensitive to this assumption.

B.3.5.1.8. Costs of Subsequent Treatments

The model does not include explicit health states for subsequent lines of treatment. However, the model does consider medication and administration costs for subsequent treatments after disease progression. For patients with non-metastatic disease who develop distant metastases without PSA progression, it was assumed that treatment with initial ADT will continue until PSA progression. Upon PSA progression leading to CRPC in either the metastatic or the non-metastatic health states (i.e., patients entering the nmCRPC and mCRPC health states), patients were assumed to continue initial ADT therapy and add an ARI – such as apalutamide, or enzalutamide. The proportions of patients receiving ARIs and chemotherapies were based on assumptions, to later be informed by clinical opinion. The model contains the functionality to continue or stop ADT alongside ARIs for both nmCRPC and mCRPC.

For patients with nmCRPC, only one line of therapy with ARIs was considered – i.e., in addition to ADT – as shown in Appendix O: Clinical parameters and variables; O1.8 Metastatic Castration-Resistant Prostate Cancer.

Patients in the mCRPC state were assumed to continue receiving ADT indefinitely. This was confirmed by clinical opinion [Personal Communication, 2023]. The utilization of post-progression therapies were assumed equal. Durations of these in CRPC were derived from published median durations of therapy from clinical trials that evaluated these therapies for metastatic CRPC (Table 135)

Table 135 in the mCRPC state, up to three lines of ARIs or chemotherapy were considered – as shown in O1.8 Metastatic Castration-Resistant Prostate Cancer; (Appendix O: Clinical parameters and variables).

B.3.5.1.9. End of Life Costs

End of life costs were taken from a widely referenced Kings Fund report by Addicott and Dewar (134). After adjusting for inflation, end of life costs were estimated to be £7070.63 and are broadly considered to represent all NHS and PSS costs incurred in the final months of life. These costs were applied for patients who die because of advanced prostate cancer (i.e., not including deaths from MACE or other causes).

B.3.5.1.10. Inflation adjustment

All costs were reported in 2022 Pounds Sterling. Published estimates based on prior year pounds were adjusted to 2022 Pounds Sterling using the Personal Social Services Research Unit Inflation Index (115).

B.3.5.2. Health-state unit costs and resource use

The cost of follow-up by health states was based on collated costs from the NHS Cost Collection (133). The monthly costs of follow-up for the non-metastatic and metastatic health states were £251.94 and £242.45, respectively. A breakdown of the follow-up costs for both health states are presented in Table 146 and Table 147 (Appendix Q: Cost and healthcare resource use identification, measurement and valuation. Section Q1.4 Health-state unit costs and resource use).

For the non-metastatic health state, the cost categories and frequencies for healthcare-resource utilisation were based on the company submission for TA580 (135), enzalutamide for treating nonmetastatic hormone-relapsed prostate cancer. The unit costs included in the tables have been obtained from the most up-to-date NHS cost collection reference source.

For the metastatic health state, the cost categories and frequencies for healthcare-resource utilization were sourced from the company evidence submission for enzalutamide for treating hormone-sensitive prostate cancer (TA712) (112). In this submission, it was stated that the frequencies were validated by clinical experts in the UK and were largely in line with the ERG report of the appraisal for enzalutamide in pre-chemo metastatic hormone-resistant prostate cancer (TA377) (136).

B.3.5.3. Adverse reaction unit costs and resource use

B.3.5.3.1. Major Adverse Cardiovascular Events (MACE)

The effects of MACE on healthcare costs include both one-off acute care costs as well as long-term chronic costs of MACE (Table 145; Appendix Q: Cost and healthcare resource use identification, measurement and valuation. Section Q1.3 Major Adverse Cardiovascular Events (MACE)). Costs of fatal and non-fatal MACE were based on estimates identified from targeted reviews of the literature. The acute and chronic costs for nonfatal MI and nonfatal other CV events were taken from a UK-based study by Danese and colleagues (131). The acute and chronic nonfatal stroke costs were taken from a UK-based study by Xu and colleagues (132) . All fatal costs were taken from the NHS Cost Collection using a weighted average of the 'Emergency medicine – dead on arrival' code (133).

B.3.5.3.2. Non-MACE Adverse Events

The costs of treatment of AEs other than MACE (per event) were assumed to be independent of treatment strategy and were taken from the NHS Cost Collection (Table 52) (133). Hot flush was assumed to have negligible or no cost in line with the assumption made in TA712 (112).

Table 52: Estimates of Direct Medical Costs for Treatment of Grade 3/4

Adverse Events	Cost per AE (£)	Cost Source
Hot flush	0	Assumed to have negligible or no cost. This assumption was made in TA712: Enzalutamide for treating hormone-sensitive metastatic prostate cancer (112).
Fatigue	144.68	NHS Cost Collection. **Currency Code**: WF01B multi-professional non-admitted face-to-face attendance first. (133).
Arthralgia	144.68	NHS Cost Collection. **Currency Code**: WF01B non-admitted face-to-face attendance first. (133).
Hypertension	770	NHS Cost Collection. **Currency Code:** EB04Z Hypertension. (133).

B.3.5.4. Miscellaneous unit costs and resource use

Not applicable.

B.3.6. Severity

The quality adjusted life year (QALY) shortfall for relugolix was calculated using the online calculator tool published by Schneider et al (137). Relugolix does not meet the criteria for a severity weight as it achieves a QALY weighting of 1. This is shown in Table 53

Table 53: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	100 % Male	Patient population (Section B.3.2.1)
Starting age	71	Patient population (Section B.3.2.1)

B.3.7. Uncertainty

We do not believe that there are any major uncertainty concerns. The use of ADT is well established in HSPC and the HERO study provided clear evidence of equivalence to existing ADT therapy on HSPC-specific outcomes.

B.3.8. Summary of base-case analysis inputs and assumptions

B.3.8.1. Summary of base-case analysis inputs

A tabulated summary of the base-case analysis inputs is provided in Appendix N: Summary of Model inputs

B.3.8.2. Assumptions

Table 54 provides a list of all assumptions in the economics model as well as justification for each assumption.

Table 54: Assumptions applied in the model

Assumption	Justification
High-risk localised subpopulation	Cost effectiveness of relugolix in the high-risk localised subpopulation subject to the recent licence extension is assumed to be the same as in the advanced HSPC population, given that the MHRA granted the licence without the requirement for supplementary trial data

	and the rate of MACE is unlikely to be different in this subgroup.
Spinal metastases subpopulation	Cost effectiveness of relugolix vs. degarelix in the subpopulation of patients with spinal metastases is assumed to be the same as in the mHSPC population.
Relative effectiveness of different GnRH agonist formulations	Different GnRH agonist formulations are assumed to have equivalent clinical efficacy, because the results of the ITC of testosterone suppression (see section B.2.9) demonstrated there to be no statistically significant differences between formulations. Furthermore, different GnRH agonist formulations were considered clinically equivalent in the NICE technology appraisal of degarelix (26).
Probabilities of PSA Progression	It was assumed that patients in the LA off-treatment state who experience PSA progression would transit to the BR state and re-initiate ADT.
Probabilities of Survival	Data on survival for patients with HSPC in HERO were not sufficient to estimate long-term survival for such patients. It was therefore assumed that mortality for nmHSPC would be the same as the general population. Survival for patients with mHSPC was derived from published estimates of the effect on survival from PSA progression in mHSPC patients versus those without PSA progression. Both of these assumptions are associated with considerable uncertainty.
Probabilities of MACE	Because the risk of MACE observed in the HERO controlled trial may not be representative of that in typical clinical practice, the probabilities of MACE in the model were based on results of an analysis of Commercially-insured patients with advanced HSPC receiving ADT in the MarketScan health insurance claims database by Brady (2020) and colleagues (138), while the RR of MACE for patients receiving GnRH antagonists versus LHRH agonists was based on the RR of such events in HERO. The definition of MACE used in the MarketScan study differed from that used in the analyses of the HERO data. Specifically, the study by Brady included “MI, cerebrovascular accident, unstable angina, thromboembolism, percutaneous coronary intervention and/or coronary bypass graft”. In contrast, HERO included “non-fatal MI, non-fatal stroke, and all-cause mortality”, though for the model, non-CV mortality was not included in the calculation of the RR, and, in point of fact, review of

	specific AEs contributing to the MACE event show that “stroke” included “cerebrovascular insufficiency”, “cerebral haemorrhage”, “carotid arteriosclerosis”, “cerebrovascular accident”, “transient ischaemic attack”, “haemorrhage intracranial”, “haemorrhagic stroke”, “carotid artery occlusion”, and “aphasia”. Because the definition of MACE in Brady was more expansive than that in HERO (e.g., Brady included “thromboembolism” and revascularization procedures whereas HERO did not, and Brady included “unstable angina” whereas HERO did not do so explicitly), this approach requires the assumption that the treatment effects on MACE in HERO can be extrapolated to the components of MACE in Brady that were not included in the HERO definition. While this assumption may be reasonable, it is associated with substantial uncertainty.
Subsequent treatment	The model assumes that an equal proportion of patients are on each available subsequent treatment due to lack of available data.
Additional medications	The model assumes that no patients receive additional medications with ADT
Disease progression	Patients in either of the LA or BR Off-treatment states with PSA progression are assumed to remain hormone-sensitive and initiate ADT again; as such, they transit to the BR On-treatment Not Castrated state. Patients in mHSPC with PSA progression are assumed to be castration-resistant and transit to the mCRPC state Patients are assumed to remain on ADT whilst they have mHSPC
History of MACE	The adjustment factor applied to the initial proportion of patients with a history of MACE to account for the impact of age (on the history of MACE) is based on US-specific data (39).
Receipt of Chemotherapy and ARI’s	The proportions of patients receiving ARIs and chemotherapies were based on assumptions.
Risk of MACE	The carry-over period for risk of MACE was based on an assumption

B.3.9. Base-case results

The primary analysis takes an NHS and PSS perspective. The ICER was calculated for the pre-defined threshold value for cost-effectiveness (willingness-to-pay [WTP] for a QALY) as per the NICE reference case (119). Costs, life years (LYs) and QALYs were reported by health state (see Appendix J: Clinical outcomes and disaggregated results from the model).

Cost-effectiveness of relugolix versus the blended GnRH agonists is summarised in Table 55 below. Relugolix is estimated to yield the joint greatest (alongside degarelix) discounted LYs ([redacted]) agonists. The ICER for relugolix is £9,489 per QALY gained compared with the blended GnRH agonists.

Table 55: Pairwise Comparisons of Cost-Effectiveness for relugolix versus Other Comparators in the Base Case

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Relugolix	[redacted]	[redacted]	[redacted]	-	-	-	-	-
GnRH agonists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,489	9,489

B.3.9.1. Base-case incremental cost-effectiveness analysis results

The results of the Incremental cost-effectiveness analyses are presented in Table 55, above, noting that degarelix is not relevant to the base case in the broader HSPC population. The ICER for relugolix vs. GnRH agonists is estimated to be £9,489 per QALY gained.

The results from the net-health benefit analysis is presented in Table 56, which shows the impact of relugolix on the modelled populations shows that there is a positive impact on their overall health when compared to the use of the blended GnRH agonists. This would result in a net increase in the health of the population being treated with relugolix.

Table 56: Net-health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Relugolix	[redacted]	[redacted]	-	-	-	-
GnRH agonists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

B.3.10. Exploring uncertainty

Sensitivity analyses are presented against the blended GnRH agonists only, as the LYs and QALY of the different GnRH agonists formulations are considered equivalent and we have taken an approach to blend GnRH agonist costs based on English prescription costs analysis data, as explained in Section B.3.5.1.3.

B.3.10.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were generated by simultaneously sampling from estimated probability distributions of model parameters. When standard errors were not reported they were calculated as 10% of the base case estimate. For each simulation, expected costs and QALYs were calculated for each comparator, along with the differences between comparators in expected costs and QALYs. Descriptive

statistics were generated based on the simulated values for costs, QALYs, incremental costs, and incremental QALYs. Ninety-five percent credible intervals were calculated for these outcomes based on the 2.5 and 97.5 percentiles of the simulations.

Cost-effectiveness acceptability curves (CEACs) were constructed for each comparator. The probabilistic ICER was calculated based on the ratio of the mean incremental cost to the mean incremental QALYs.

Outputs from the probabilistic sensitivity analysis iterations is presented as scatter points on the cost effectiveness plane in [redacted]
points, which represent the simulated incremental costs and QALYs, are in the northeast quadrant, a majority lie beneath the willingness to pay threshold line of £20,000/QALY. This indicates that any uncertainty associated with the ICER still lies within the bounds of cost-effectiveness. The probabilistic ICER of £9,640 was higher than the deterministic ICER of £9,489, it still falls well within the bounds of NICE's lowest willingness to pay threshold of £20,000 per QALY.

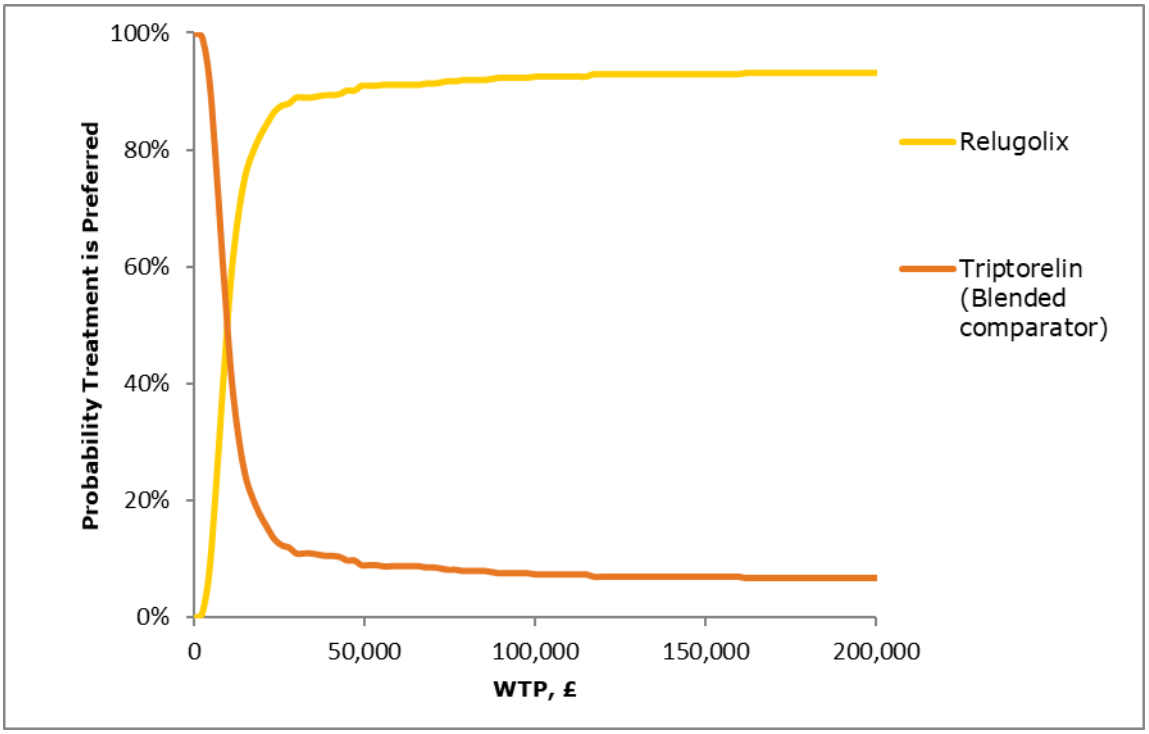
Table 57: Probabilistic cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Relugolix CT	[redacted]	[redacted]	[redacted]	-	-	-	-	-
GnRH agonists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,640	9,640

[redacted]

The probabilistic sensitivity analyses results were also plotted in the form of a cost-effectiveness acceptability curve (CEAC). The CEAC shows the probability of cost effectiveness for relugolix and GnRH agonist given varying willingness to pay thresholds for a QALY. According to the CEAC, the probability of relugolix being cost-effective is 82% at a willingness to pay of £20,000/QALY (Figure 23).

Figure 23: Cost effectiveness acceptability curve - relugolix vs. GnRH Agonist (Blended)



B.3.10.2. Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were undertaken to explore the impact of changing assumptions concerning key model parameter values on the ICER. These sensitivity analyses included both one-way deterministic sensitivity analyses (OWSA), in which a numerical variable is varied over a specified range in order to measure its impact on cost-effectiveness, and scenario analyses in which results are evaluated for a particular set of assumptions and parameter estimates. Parameters included in the OWSA were varied by +/-25% of base case estimates and presented in tornado plots. Based on results of the model, estimates of cost-effectiveness were most sensitive to varying parameters related to MACE, utility and treatment discontinuation. Specifically, the most influential parameters were as follows:

1. Health state utilities for biochemical recurrence, being castrate as well as for those locally advanced.

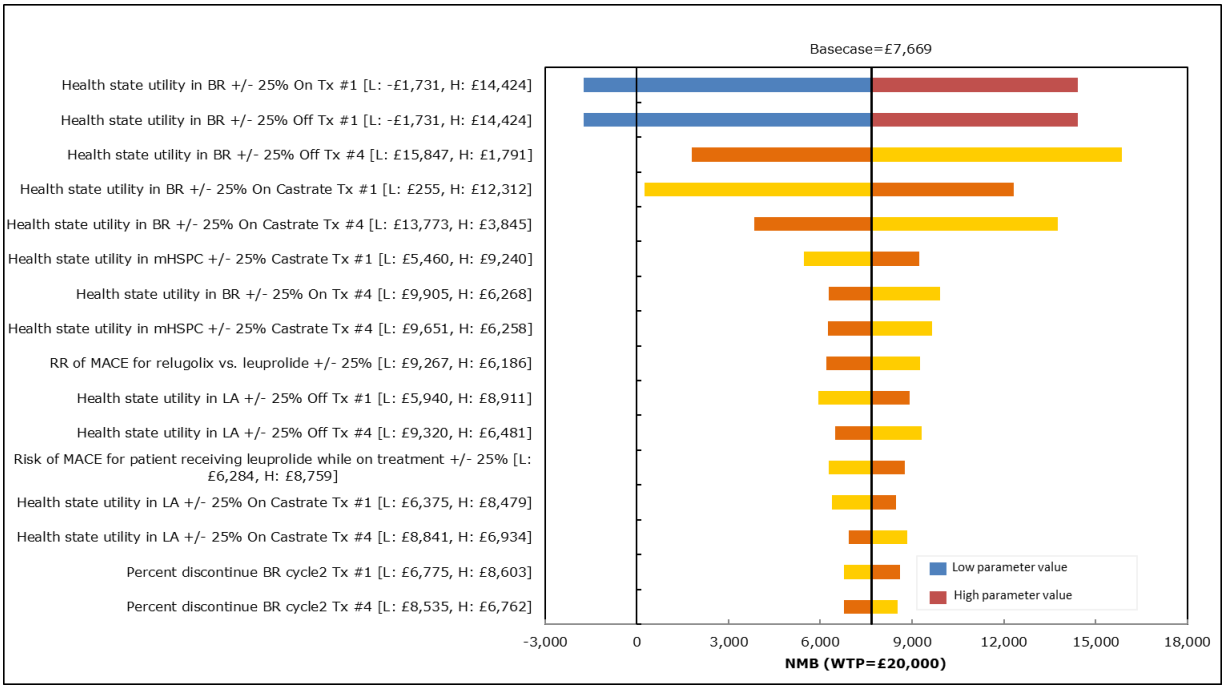
2. Relative risk of MACE for relugolix vs. leuprolide (Triptorelin blended comparator)

3. Risk of MACE for patients receiving leuprolide or other LHRH agonists while on treatment; and

4. Percent of Biochemically-Recurrent Patients discontinuing by Time since Initiation of Therapy

These parameters, as well as costs of medication acquisition, costs of MACE, costs of healthcare resources for follow-up and monitoring, and other health state utility values were included in the tornado analyses. Only the 15 most influence parameters in the model are presented in the DSA. The tornado diagram below (Figure 24) shows the analysis results of relugolix vs triptorelin (blended comparator).

Figure 24: Tornado Diagram - Relugolix vs Triptorelin (blended comparator)



B.3.10.3. Scenario analysis

The model also includes functionality to conduct scenario analyses, in which model results are generated for alternative sets of assumptions. The sensitivity of the model results to changes in key assumptions was examined and include the following scenarios:

1. Exploring a range of durations for the carry-over period for MACE – including no carry-over and 12 months.

2. An assumption that patients no longer continue receiving initial ADT after failure to achieve castration and would subsequently be at increased risk of PSA progression

3. Adverse event utilities were removed from the model to determine their impact; and

4. Exclusion of MACE

The scenario analyses are presented below with pairwise ICERs presented for relugolix vs leuprolide. The ICER estimates for each of the scenario analyses result in higher ICERs, except for the No MACE impact analysis. These ICERs lie close to the base case.

The scenario which has the highest impact is the No MACE assumption. It resulted in a small increase in cost in the relugolix arm, leading to being dominated by Triptorelin (blended comparator). The exclusion of AEs had the smallest impact on the ICER, generating the same incremental cost of relugolix as in the base case analysis, as well as more QALYs. Resulting in very small change in the ICER compared to the base case.

The scenario which had the second largest impact on the ICER was whether patients continued ADT therapy after becoming castrate resistant. However, this has marginal impact on the overall incremental QALYs and resultant ICER, compared to the base case.

Table 58: Results of Scenario analyses

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs	Incremental QALYs	ICER vs. relugolix
Base-case			[redacted]	[redacted]	**£9,489**
Carry over period of MACE	6.8	Reducing the carry over risk of MACE to:			
		0 months	[redacted]	[redacted]	£9,935
		12 months	[redacted]	[redacted]	£9,444
Adverse event disutility	Included	Excluded	[redacted]	[redacted]	£9,440
ADT treatment continuation after castrate resistance	yes	Patients no longer receive ADT therapy after becoming castrate resistant (non-metastatic or metastatic PC)	[redacted]	[redacted]	£9,362
No Impact of MACE	RR of MACE	No MACE impact	[redacted]	[redacted]	£ Dominated

B.3.11. Subgroup analysis

Subgroup analysis was carried out against degarelix, which was considered for patients with spinal metastases in NICE TA404 and the blended GnRH agonists in the mHSPC subpopulation.

The model population was restricted to mHSPC patients only. The initial health state probabilities were based on disease characteristics for patients enrolled in the HERO trial and reweighted to include both castrated and not castrated only. The RR of MACE as well as the percentage of the population who achieved castration was updated using NMA data which included degarelix (see Table 37). Table 59 below presented the results comparing relugolix, degarelix and the blended GnRH agonists directly.

Relugolix is estimated to generate lower LYs and QALYs compared to degarelix ([redacted]).
Relugolix therefore would result in a cost saving of around £51,887 per QALY. This generates an ICER of £51,887 in the southwest quadrant. As ICERs above the willingness to pay threshold are cost effective in this quadrant, this demonstrates relugolix to be cost effective within NICE's range. This is further supported by the positive net health benefit (NHB) results in Table 60.

Compared to the GnRH agonist (blended comparator), relugolix generated higher LY's and QALY ([redacted]).
results in a cost per QALY of £9,288 in the same metastatic population. This is lower than the cost per QALY of £15,639 for degarelix in the same population.

Table 59: Incremental cost effectiveness results in metastatic subpopulation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
GnRH agonists	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,288	9,288
Degarelix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,639	51,887

Table 60: Pairwise Net health benefit (relugolix vs. comparator) in metastatic subpopulation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Relugolix	[redacted]	[redacted]	-	-	-	-
Degarelix	[redacted]	[redacted]	[redacted]	[redacted]	0.09	0.04
GnRH agonists	[redacted]	[redacted]	[redacted]	[redacted]	0.16	0.21

B.3.12. Benefits not captured in the QALY calculation

We believe that the majority of benefits have been captured in the QALY calculation. Some patients have needle phobia/anxiety regarding injections, will may lead to additional disutility not currently captured in the GnRH agonist arm.

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

The quality assessment (QA) and validation of the economic model was performed through different steps by two independent reviewers. First, the overall quality of the economic evaluation was assessed using the British Medical Journal (BMJ) checklist, as provided in the guidelines for authors and peer reviewers of economic submissions to the BMJ (139). The QA after adaptation for the English and Welsh population was conducted in two parts. Firstly, the model underwent a full quality assessment using custom validation procedures to ensure the model was structually and functonally sound. Secondly. cell-by-cell checks were made on inputs as well as using another internal checklist to ensure the model performed as expected when performing these.

Additionally, an adapated version of the TECH-VER (technical verification) checklist (140) was used to identify model implementation errors and their root causes. The TECH-VER checklist is a comprehensive checklist for the technical verification of decision analytical models, aiming to help identify model implementation errors and their root causes while improving the transparency and efficiency of the verification efforts.

Finally, the model survival predictions were compared with UK prostate cancer data (see Appendix J).

B.3.14. Interpretation and conclusions of economic evidence

Relugolix is a cost-effective option for treatment of HSPC individuals, Compared to GnRH agonists, relugolix both increased the LY's and QALY's gained from treatment. This resulted in a cost per QALY of £9,489, which is well within NICE's lowest willingness to pay threshold. The key uncertainty underpinning the ICER was

the effect in preventing MACE. However, even without an effect on MACE, relugolix has cost benefits from reducing the need for injections, a benefit which would also free NHS resource.

Relugolix was cost saving in the subgroup of patients with spinal metastases when compared to degarelix, generating an ICER in the southwest quadrant that was cost effective. Relugolix would provide an additional treatment for these patients, who currently only have degarelix as an alternative to GnRH agonist, which requires monthly injection and has been associated with painful injection site reactions (141).

B.4. References

1. Crawford ED, Schally AV, Pinthus JH, Block NL, Rick FG, Garnick MB, et al., editors. The potential role of follicle-stimulating hormone in the cardiovascular, metabolic, skeletal, and cognitive effects associated with androgen deprivation therapy. Urologic Oncology: Seminars and original investigations; 2017: Elsevier.
2. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. Journal of the National Cancer Institute. 2010;102(1):39-46.
3. Plummer C, Collins P, Rosario DJ, Kirby M, Jain S, Davey P, et al. Managing cardiovascular risk in high-risk prostate cancer. Trends in Urology & Men's Health. 2017;8(6):13-8.
4. Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating NL, Van Hemelrijck M. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol. 2015;68(3):386-96.
5. Gandaglia G, Sun M, Popa I, Schiffmann J, Abdollah F, Trinh QD, et al. The impact of androgen-deprivation therapy (ADT) on the risk of cardiovascular (CV) events in patients with non-metastatic prostate cancer: a population-based study. BJU international. 2014;114(6b):E82-E9.
6. Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. Circulation. 2010;121(6):833-40.
7. Margel D, Peer A, Ber Y, Shavit-Grievink L, Tabachnik T, Sela S, et al. Cardiovascular morbidity in a randomized trial comparing GnRH agonist and GnRH antagonist among patients with advanced prostate cancer and preexisting cardiovascular disease. The Journal of Urology. 2019;202(6):1199-208.
8. Nascimento B, Miranda EP, Jenkins LC, Benfante N, Schofield EA, Mulhall JP. Testosterone recovery profiles after cessation of androgen deprivation therapy for prostate cancer. The journal of sexual medicine. 2019;16(6):872-9.
9. Cancer Research UK. Prostate cancer incidence statistics Cancer Reseearch UK; 2018 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer.
10. Rawla P. Epidemiology of Prostate Cancer. World J Oncol. 2019;10(2):63-89.
11. Mayor S. PSA screening significantly cuts risk of death from prostate cancer, review finds. British Medical Journal Publishing Group; 2017.
12. Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al. Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2023;388(17):1547-58.
13. Steele CB, Li J, Huang B, Weir HK. Prostate cancer survival in the United States by race and stage (2001-2009): findings from the CONCORD-2 study. Cancer. 2017;123:5160-77.
14. Bhatia N, Santos M, Jones LW, Beckman JA, Penson DF, Morgans AK, et al. Cardiovascular effects of androgen deprivation therapy for the treatment of prostate cancer: ABCDE steps to reduce cardiovascular disease in patients with prostate cancer. Circulation. 2016;133(5):537-41.

15. Cereda V, Falbo PT, Manna G, Iannace A, Menghi A, Corona M, et al. Hormonal prostate cancer therapies and cardiovascular disease: a systematic review. Heart Failure Reviews. 2022;27(1):119-34.
16. O'Farrell S, Garmo H, Holmberg L, Adolfsson J, Stattin P, Van Hemelrijck M. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2015;33(11):1243-51.
17. Satariano WA, Ragland KE, Eeden SKVD. Cause of death in men diagnosed with prostate carcinoma. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1998;83(6):1180-8.
18. Moustsen IR, Larsen SB, Duun-Henriksen AK, Tjønneland A, Kjær SK, Brasso K, et al. Risk of cardiovascular events in men treated for prostate cancer compared with prostate cancer-free men. British journal of cancer. 2019;120(11):1067-74.
19. Cancer Research UK. Cancer Research UK statistics for prostate cancer 2022 [Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/.
20. Moul JW. The evolving definition of advanced prostate cancer. Reviews in urology. 2004;6(Suppl 8):S10.
21. Huggins C, Stevens R, Hodges CV. Studies on prostatic cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Archives of surgery. 1941;43(2):209-23.
22. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management (NG131) 2019 [Available from: https://www.nice.org.uk/guidance/ng131.
23. European Association of Urology. Prostate cancer clinical guidelines [Available from: https://uroweb.org/guidelines/prostate-cancer/chapter/treatment.
24. European Society for Medical Oncology. Clinical Practise Guidelines-Prostate Cancer [Available from: https://www.esmo.org/guidelines/guidelines-by-topic/genitourinary-cancers/prostate-cancer.
25. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. 2021.
26. National Institute for H, Care E. Degarelix for treating advanced hormone-dependent prostate cancer (TA404) 2016 [
27. Abufaraj M, Iwata T, Kimura S, Haddad A, Al-Ani H, Abusubaih L, et al. Differential impact of gonadotropin-releasing hormone antagonist versus agonist on clinical safety and oncologic outcomes on patients with metastatic prostate cancer: a meta-analysis of randomized controlled trials. European Urology. 2021;79(1):44-53.
28. Sari Motlagh R, Abufaraj M, Mori K, Aydh A, Rajwa P, Katayama S, et al. The Efficacy and Safety of Relugolix Compared with Degarelix in Advanced Prostate Cancer Patients: A Network Meta-analysis of Randomized Trials. European Urology Oncology. 2021.
29. Mcleod DG. Hormonal therapy: historical perspective to future directions. Urology. 2003;61(2):3-7.
30. Oh WK, Landrum MB, Lamont EB, McNeil BJ, Keating NL. Does oral antiandrogen use before leuteinizing hormone-releasing hormone therapy in patients with metastatic prostate cancer prevent clinical consequences of a testosterone flare? Urology. 2010;75(3):642-7.
31. Bubley GJ. Is the flare phenomenon clinically significant? Urology. 2001;58(2):5-9.

32. Mahler C. Is the flare phenomenon clinically significant? Cancer. 1993;72(S12):3799-802.
33. Thompson IM. Flare associated with LHRH-agonist therapy. Reviews in urology. 2001;3(Suppl 3):S10.
34. European Medicines Compendium. Casodex 50 mg Film-coated Tablets 2020 [Available from: .
35. Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS, et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer. 2007;110(7):1493-500.
36. FDA U. FDA drug safety communication: Update to ongoing safety review of GnRH agonists and notification to manufacturers of GnRH agonists to add new safety information to labeling regarding increased risk of diabetes and certain cardiovascular diseases 2010 [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-update-ongoing-safety-review-gnrh-agonists-and-notification.
37. Lopes RD, Higano CS, Slovin SF, Nelson AJ, Bigelow R, Sørensen PS, et al. Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: the primary results of the PRONOUNCE randomized trial. Circulation. 2021;144(16):1295-307.
38. Shore ND, Saad F, Cookson MS, George DJ, Saltzstein DR, Tutrone R, et al. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer. N Engl J Med. 2020;382(23):2187-96.
39. Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. European urology. 2014;65(3):565-73.
40. Cirne F, Aghel N, Petropoulos JA, Klotz L, Lenihan DJ, Saad F, et al. The Cardiovascular Effects of Gnrh Antagonists in Men with Prostate Cancer. Eur Heart J Cardiovasc Pharmacother. 2021.
41. Gu L, Li X, Liu W. Adverse cardiovascular effect following gonadotropin-releasing hormone antagonist versus GnRH agonist for prostate cancer treatment: A systematic review and meta-analysis. Frontiers in Endocrinology. 2023;14.
42. Electronic Medicines Compendium. Firmagon 80mg Injection 2022 [Available from: https://www.medicines.org.uk/emc/product/6535/smpc.
43. Sciarra A, Fasulo A, Ciardi A, Petrangeli E, Gentilucci A, Maggi M, et al. A meta-analysis and systematic review of randomized controlled trials with degarelix versus gonadotropin-releasing hormone agonists for advanced prostate cancer. Medicine. 2016;95(27).
44. Doehn C, Sommerauer M, Jocham D. Degarelix for prostate cancer. Expert Opinion on Investigational Drugs. 2009;18(6):851-60.
45. European Medicines Compendium. Prostap 3 DCS [Available from: .
47. European Medicines Agency. Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data . INN: leuprorelin-containing depot medicinal products 2020 [Available from: https://www.ema.europa.eu/en/documents/referral/leuprorelin-containing-depot-medicines-article-31-referral-public-assessment-report-prac_en.pdf.
48. Delgado J, Ory J, Loloi J, Deebel NA, Bernstein A, Nackeeran S, et al. Persistent Testosterone Suppression After Cessation of Androgen Deprivation Therapy for Prostate Cancer. Cureus. 2022;14(12).

49. Crawford ED, Heidenreich A, Lawrentschuk N, Tombal B, Pompeo AC, Mendoza-Valdes A, et al. Androgen-targeted therapy in men with prostate cancer: evolving practice and future considerations. Prostate cancer and prostatic diseases. 2019;22(1):24-38.
50. Accord Healthcare dof. Patient Preference Study Prostate Cancer 2023.
51. National Institute for H, Care E. Prostate cancer: diagnosis and management (NG131) 2019 [Available from: https://www.nice.org.uk/guidance/ng131.
52. European Society for Medical O. Clinical Practise Guidelines-Prostate Cancer [Available from: https://www.esmo.org/guidelines/guidelines-by-topic/genitourinary-cancers/prostate-cancer.
53. Dearnaley DP, Saltzstein DR, Sylvester JE, Karsh L, Mehlhaff BA, Pieczonka C, et al. The Oral Gonadotropin-releasing Hormone Receptor Antagonist Relugolix as Neoadjuvant/Adjuvant Androgen Deprivation Therapy to External Beam Radiotherapy in Patients with Localised Intermediate-risk Prostate Cancer: A Randomised, Open-label, Parallel-group Phase 2 Trial. European Urology. 2020;78(2):184-92.
54. Shore ND, Bailen JL, Pieczonka C, Saltzstein DR, Sieber PR, MacLean DB, et al. PD28-01 testosterone lowering, PSA response and quality of life in patients with advanced hormone sensitive prostate cancer receiving TAK-385, an oral GnRH antagonist: phase 2 interim analysis. The Journal of Urology. 2016;195(4S):e654-e.
55. Saad F, Bailen JL, Pieczonka CM, Saltzstein DR, Sieber PR, Maclean DB, et al. Second interim analysis (IA2) results from a phase II trial of TAK-385, an oral GnRH antagonist, in prostate cancer patients (pts). American Society of Clinical Oncology; 2016.
56. MacLean DB, Shi H, Faessel HM, Saad F. Medical Castration Using the Investigational Oral GnRH Antagonist TAK-385 (Relugolix): Phase 1 Study in Healthy Males. The Journal of Clinical Endocrinology & Metabolism. 2015;100(12):4579-87.
57.
https://bnf.nice.org.uk/drug/leuprorelin-acetate.html.
https://www.medicines.org.uk/emc/product/4651/smpc.
https://www.nice.org.uk/guidance/ta412.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Summary of Information for Patients (SIP)

January 2024

File name	Version	Contains confidential information	Date
ID6187 Relugolix vi. SIP [noCON]	1.0	Yes	24.01.24

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response: Relugolix (Orgovyx™)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response: Orgovyx is indicated: • For the treatment of adult patients with advanced hormone-sensitive prostate cancer. • For the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy. • As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response: Relugolix first received marketing authorisation from the European Medicines Agency on 29th April 2022 and UK Medicines Agency and Healthcare products Regulatory Agency (MHRA) on 17th June 2022. The original marketing authorisation was for the "treatment of adult patients with advanced, hormone-sensitive prostate cancer (locally advanced, metastatic, including biochemical relapse)." MHRA has since approved a marketing authorisation variation application from Accord to include the following subgroups: • "high-risk localised and locally advanced hormone-sensitive prostate cancer in combination with radiotherapy.

- As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone-sensitive prostate cancer."

The update to the MHRA marketing authorisation was published on 28th December 2023 and can be found here:
https://mhraproducts4853.blob.core.windows.net/docs/14cac18aebcf435b6e6b288b157528c688adf114

Locally advanced prostate cancer is cancer that has started to break out of the prostate, or has spread to the area just outside the prostate (https://prostatecanceruk.org/prostate-information-and-support/just-diagnosed/locally-advanced-prostate-cancer).

Metastatic prostate cancer is cancer that has spread from the prostate to other parts of the body and is interchangeably known as advanced or metastatic prostate cancer. It develops when prostate cancer cells move through the blood stream or lymphatic system (https://prostatecanceruk.org/prostate-information-and-support/just-diagnosed/advanced-prostate-cancer).

Localised prostate cancer is cancer that is inside the prostate and hasn't spread to other parts of the body. Localised prostate cancer can be additionally categorised as low, medium or high risk, which relates to the risk of the cancer spreading. To work out this risk, doctors may look at your prostate specific antigen (PSA) level, your Gleason score (or grade group) and the T stage of your cancer. These factors will place you in one of five categories in the Cambridge Prognostic Group (CPG). High-risk disease is usually used to describe CPG groups 4 and 5. A description of the various measures used to establish this categorisation can be found in the Prostate Cancer UK Localised Prostate Cancer fact sheet (https://shop.prostatecanceruk.org/pdf/publication/localised-prostate-cancer_ifm.pdf).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:
Accord has worked with TACKLE (patient group) on a patient perspective study. Financial support was provided at a value of £5,000. This accounted for consultation and independent input into the design of the interview script and online questionnaire as part of the steering committee alongside the HCPs, support in raising awareness in their network to aid recruitment, and appraisal of the results/analysis.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

Prostate cancer is a malignant tumour of the prostate, a male reproductive gland found below the bladder. It is the most common cancer in males in the UK, accounting for 52,000 new cases each year and over 12,000 deaths (https://www.cancerresearchuk.org/about-cancer/prostate-cancer). In England, more than 44,000 men are diagnosed with prostate cancer and more than 10,000 men die every year. Approximately, 420,000 men are living with or after prostate cancer in England (https://prostatecanceruk.org/prostate-information-and-support/risk-and-symptoms/about-prostate-cancer) and as a consequence everyday life is affected emotionally as well as physically. Side effects after treatment are common. For example, after prostatectomy, 9% of men develop genitourinary complications which require further investigation or treatment 2 years after radical treatments (NICE impact prostate cancer (https://www.nice.org.uk/about/what-we-do/into-practice/measuring-the-use-of-nice-guidance/impact-of-our-guidance/nice-impact-prostate-cancer). Overall, survival rates for prostate cancer are high (97%) if the cancer is caught early and has not spread beyond the prostate [1] but these rates decrease dramatically when the cancer has spread, with a 5-year survival rate ranging from 26% to 30% [2].

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

Prostate cancer is classified on whether, and how far the cancer has spread. When prostate cancer spreads beyond the prostate or is at high risk of progression or returns after initial treatment, it is called advanced prostate cancer. The diagnosis of advanced prostate cancer is made using the results of some or all of the following tests:

- by assessing the levels of prostate specific antigen* in the blood
- a biopsy of prostate tissue
- scans to see how big the cancer is and how far it has spread, which can include digital rectal examination (DRE), magnetic resonance imaging (MRI), computerised tomography (CT), bone scans, or positron emission tomography (PET) scans.

More information on the tests used to diagnose advanced prostate cancer can be found here: https://prostatecanceruk.org/prostate-information-and-support/just-diagnosed/advanced-prostate-cancer

No additional diagnostic tests would be required for the use of relugolix.

*Prostate specific antigen is a protein produced by both normal and cancerous prostate cells. It is usually present in the blood at low levels. High levels of PSA in the blood may mean that there is a problem with the prostate, in other words, it can be a marker of the health of the prostate.

In some men, a raised PSA level is due to cancer, but in most men, it means the prostate has grown in size without this being caused by cancer. An increase in blood PSA levels while a man is having treatment for prostate cancer could mean that the cancer has started to worsen and grow again. A decrease in blood PSA levels while a man is having treatment for prostate cancer can tell doctors that the treatment is working.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

The main stay of treatment in patients with prostate cancer is hormone therapy (also called androgen deprivation therapy). At first, prostate cancer cells rely on male sex hormones, such as testosterone, to grow. Treatment for prostate cancer involves lowering testosterone levels through hormone therapy (called chemical castration). Androgen deprivation therapy (ADT) is usually combined with other therapies, such as radiotherapy where there is evidence that the cancer is at risk of spreading or to manage patients that have relapsed [3].

Where there is evidence that the cancer is still progressing (metastatic prostate cancer, e.g. the cancer is spreading to other parts of the body), androgen deprivation therapy is usually continued. NICE recommends androgen deprivation therapy as the first treatment option for patients diagnosed with metastatic prostate cancer in combination with other medications, for example enzalutamide or docetaxel (a chemotherapy) [3].

The androgen deprivation therapy class can be split into two types of drugs: gonadotrophin releasing hormone (GnRH) agonists, and GnRH antagonists. GnRH agonists include the drugs leuprorelin, goserelin, triptorelin, and buserelin. These GnRH agonists are used interchangeably by doctors to treat prostate cancer, as they all have similar levels of clinical effectiveness. Currently, there is only one GnRH antagonist recommended for use in the UK, which is called degarelix. Degarelix is only recommended in a small subgroup of advanced prostate cancer patients with spinal metastases [4].

All the above treatments are injections that have to be given by a nurse in a clinical setting. Relugolix is the only androgen deprivation therapy available as an oral medicine that can be taken at home.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

Accord Healthcare have sponsored research to understand the patient's perspective (referred to here as study 1) on the way they were involved in treatment decisions (in particular androgen deprivation therapy) and their needs in terms of follow-up and counselling. As relugolix is the first

oral androgen deprivation therapy, a second study (referred to here as study 2) was undertaken to understand the preference of patients if they are offered different androgen deprivation therapy options (for example oral versus injectable treatment).

Study 1: 19 patients diagnosed with advanced prostate cancer were recruited through a patient advocacy organisation to complete a 60-minute questionnaire. Patients were asked to map out their patient journey highlighting key events which occurred during their journey (diagnosis to present day). The key findings from this study are outlined below:
1. Most androgen deprivation therapy challenges relate to side effects, such as hot flushes, sexual side effects, fatigue, mood and weight gain. Patients require more proactive discussions and signposting to support services and therapies – especially around sexual side effects.
2. The second key finding was patients find organising androgen deprivation therapy injections can be inconvenient and stressful. For example, patients worry they will forget to arrange their injections or that an ineffective booking system will result in their injections being missed.
3. Receiving injections is painful but patients are accepting of this given androgen deprivation therapy is considered a life-saving treatment and administered relatively infrequently.
4. The cancer nurse specialist plays an important role in offering follow-up androgen deprivation therapy support.
5. There is a lot of beneficial support provided by patient support groups and charities but there is inconsistent health-care professional sign-posting to these services.
6. Not all patients want to engage in counselling services but believe it should be offered free as part of a care package.
7. There is a cohort of patients that would prefer more involvement in their hormone therapy treatment decisions.
8. Androgen deprivation therapy side effects persist months after treatment cessation, impacting patients' quality of life
9. Variable NHS services impact on the patient's experience.

Study 2. 48 patients diagnosed with advanced prostate cancer were recruited via a patient advocacy organisation to complete a 20-minute online survey. Attributes selected as the most preferred and the least preferred were scored. The data showed that patients prefer 3-monthly injections with a large cohort of patients preferring oral androgen deprivation therapy (40%). Patients also valued treatments that were associated with a faster testosterone recovery and that were effective quicker. No requirement to book an appointment with a doctor or a nurse for administration of treatment was also an important attribute.

The most preferred attributes were a therapy used by doctors for a long time, injections administered every 3 months, a faster testosterone recovery after treatment discontinuation, a quicker onset of action, and an oral formulation.
Although, all types of ADT used by participants were injectables, 40% of the sample indicated a preference for an oral ADT through the MaxDiff. questions.
In part 2, 63% of patients chose relugolix as the preferred ADT when presented the blinded treatment options. The most common reason for selecting relugolix was oral administration, followed by speed of testosterone recovery and least impact on their daily lives.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Relugolix is a type of androgen deprivation therapy and acts to lower the levels of testosterone in men with advanced prostate cancer. To do this, relugolix changes the actions of a hormone in the brain called gonadotrophin releasing hormone (or GnRH). GnRH instructs the brain to produce luteinizing hormone (LH) which then tells the testicles to make testosterone. Relugolix stops the release of GnRH which ultimately lowers the release of testosterone from the testes.

There are two types of androgen deprivation therapy and they differ in the way they affect GnRH. Relugolix is a GnRH antagonist. This means that it directly blocks GnRH signalling in the brain and quickly lowers the levels of testosterone (within days).

The other type of androgen deprivation therapy is called a GnRH agonist. This means that it mimics GnRH and signals the testicles to make testosterone. As a result, most men experience a testosterone flare at the start of treatment with a GnRH agonist. This flare can make symptoms worse, and often requires additional treatment. Over time the brain becomes less sensitive to GnRH signals and this leads to luteinizing hormone and testosterone levels dropping.

Although GnRH agonists are the mainstay of treatment in the UK, there are safety concerns associated with them. In 2010, the US Food and Drug Administration (FDA) issued a notification to add new safety warnings on GnRH agonist labels warning of an increased risk of diabetes, heart attack, sudden cardiac death, and stroke [5]. Similar advisory statements were published by the American Cancer Society and American Urological Association [6].

Relugolix is also the first oral GnRH antagonist. All other treatment options require injection by a nurse which can be time-consuming and stressful for patients. Injections can be painful, and skin reactions at the injection site are common.

The other unique advantage of relugolix is the fast recovery in testosterone levels once treatment has stopped. This could be particularly beneficial as the side effects associated with low testosterone can impact on the everyday life of patients.

The patient information leaflet for relugolix can be found here:
https://mhraproducts4853.blob.core.windows.net/docs/9a461baa0e2248397902be06c07adc358f85f637

A summary of the product characteristics for relugolix can be found here:
https://mhraproducts4853.blob.core.windows.net/docs/14cac18aebcf435b6e6b288b157528c688adf114

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:
Relugolix can be used in combination with other medicines as part of usual treatment. Relugolix can be used in combination with radiotherapy in:

- People with high-risk prostate cancer
- People with cancer that has spread just beyond the prostate (locally advanced)
- People whose disease has progressed after treatment.

For people offered radiotherapy, large clinical trials show that bowel function will be affected as a result of the radiotherapy in 5 out of 100 patients (https://www.nice.org.uk/guidance/ng131).

For people with newly diagnosed metastatic disease, NICE recommends starting docetaxel chemotherapy within 12 weeks of starting androgen deprivation therapy such as relugolix (https://www.nice.org.uk/guidance/ng131) . A large UK clinical trial found that 15 out of 100 people developed a fever because the chemotherapy (docetaxel) had reduced their ability to fight infection and 8 out of 100 people felt usually weak or tired https://www.nice.org.uk/guidance/ng131/chapter/Recommendations#metastatic-prostate-cancer.

Additional options for treating metastatic prostate cancer, in combination with androgen deprivation therapy (such as relugolix) include enzalutamide or apalutamide (if docetaxel is not suitable), and darolutamide with docetaxel. These agents are another form of hormone therapy that prevent the androgen receptor from working, which helps slow down the growth of the cancer. The most frequently reported side effects are hot flushes & tiredness. Severe side effects include, high blood pressure and low white cell count which makes patients more likely to get an infection (https://www.nice.org.uk/guidance/ta712/chapter/1-Recommendations).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:
Relugolix is taken orally. Patients should take 360 mg (three tablets) on the first day of treatment followed by a 120 mg (one tablet) dose once a day at approximately the same time each day. The treatment duration depends upon the disease stage and how severe the disease is. This is the case for treatment with any androgen deprivation therapy.

Existing androgen deprivation therapies are given by injection (see section 3a) which can be inconvenient and stressful for patients. Injections are administered by a nurse and the responsibility is on the patient to book each treatment appointment. This disrupts everyday life and may require patients to take time off work as well as incurring travel costs.

One of the most common side effects with injectable androgen deprivation therapies is pain or skin reactions around the injection site. The only currently recommended GnRH antagonist,

degarelix, is administered by monthly injection and requires a large injection volume (6ml for the first injection and 4 mL afterwards). Use of degarelix has been limited, possibly due to the rate of reactions around the injection site (44%) [7].

One of the most commonly used GnRH agonists is leuprolide. It is administrated every 3 to 6 months (0.375 mL for the 22.5 mg 3-month depot injection) [8]. Whilst the risk of injection site reactions is lower with leuprolide (< 1%), they are still regarded as occurring at a frequency of either very common or common [9, 10]. The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) [11] has recommended that only healthcare professionals familiar with the preparation steps for these injectable medicines should prepare and administer them to patients. This is because of reports of handling errors. The review found that handling errors resulted in some patients receiving insufficient amounts of their medicine (too much or too little).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

1. The HERO trial (Clinical Trial Identifier NCT03085095).

The phase 3 HERO study compared how well relugolix and leuprolide worked in lowering blood testosterone to sustained castration levels in men with advanced prostate cancer. Castration levels of testosterone are when blood testosterone levels fall below 50 ng/dl. Sustained castration is a blood testosterone level below 50 ng/dl from Day 29 through 48 weeks of treatment. Profound castration levels of testosterone are when blood testosterone levels fall below 20 ng/dl.

HERO was a global study and included men from 21 countries (including 4 study sites in the UK). All the men who took part in the HERO study:

- Were 18 years of age or older
- Were eligible to take study medication for at least 1 year
- Had advanced prostate cancer, for which hormone therapy was the next appropriate treatment option:
    - Cancer that has relapsed (grown in size or shown an increase in prostate specific antigen levels after initial therapy such as surgery or radiation therapy,
    - Locally advanced cancer for which local therapy was not likely to work, or
    - Newly diagnosed metastatic cancer that was likely to respond to hormone therapy.

Men could not take part in the HERO study if they had experienced serious medical problems such as a heart attack or stroke within the last 6 months. Men previously treated with docetaxel or expected to receive docetaxel were not able to take part. Men receiving androgen deprivation therapy either before or after radiotherapy were also not able to take part.

A total of 930 men who took part in the HERO study received at least one dose of study medication and were included in the analyses. All men were given one of two medicines:

- Relugolix (360 mg first dose, then 120 mg once every day by mouth)
- Leuprolide (22.5 mg every 3 months by injection (lower dose of 11.25 mg used in Japan and Taiwan)

Treatment was given for up to 48 weeks. Men whose cancer got worse or had increasing blood prostate specific antigen level, even though their testosterone had dropped to castration levels, could receive additional cancer treatment.

A full plain language summary of this trial can be found here:
https://www.futuremedicine.com/doi/10.2217/fon-2022-0172

The results from this trial were also published in the New England Journal of Medicine [12].
Completion Date: 25.11.2021

2. C27003 (Clinical Trial Identifier NCT02083185).
This Phase 2 trial compared relugolix with degarelix (another androgen deprivation therapy that works similarly to relugolix) for 24 weeks. Men with intermediate and high-risk prostate cancer who required androgen deprivation therapy with radiotherapy were included in this trial. 103 men were enrolled in the study from 23 centres in the US and five sites in the UK. The results from this trial were published in European Urology [13]. Completion Date: 12.2015.

3. Apa-RP [A Study of Apalutamide (Adjuvant Treatment) and Androgen Deprivation Therapy (ADT) in Participants Who Have Undergone Radical Prostatectomy (RP) for Non-metastatic Prostate Cancer and Who Are at High Risk for Metastases] (Clinical Trial Identifier NCT04523207).
This Phase 2 study evaluated the rate of recurrence (e.g. how often cancer returns) in patients with high-risk localised prostate cancer following radical prostatectomy (surgical removal of the prostate) who receive apalutamide with androgen deprivation therapy (included 12 patients with relugolix). The trial enrolled 108 men in locations around the US and completed on 25.10.2023. The results are published in Targeted Oncology [14].

4. Evaluating relugolix in combination with abiraterone or apalutamide. (Clinical Trial Identifier NCT04666129).
This study is based in the United States and is a 52-week, safety and tolerability study of relugolix in combination with abiraterone with a corticosteroid (Part 1), or apalutamide (Part 2). Eligible patents include those with metastatic prostate cancer. The estimated study completion date was November 2023, however no additional information was available at the time of writing this as Accord are not the sponsors of this study. Patients completing ≥12 weeks were included in an interim report, published in Targeted Oncology [15].

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

HERO study

The aim of the HERO study was to find out how well relugolix works, compared with leuprolide, in men with advanced prostate cancer. Researchers found at Day 15 of treatment, 99% of the men taking relugolix had achieved castration levels of testosterone whereas only 12% of men receiving leuprolide had achieved castration levels of testosterone. The results at Day 15 are what would be expected from the different ways in which relugolix and leuprolide work – leuprolide causes an initial surge in testosterone levels before they decrease.

When testosterone was measured at Day 29, 97% of men who received relugolix achieved and maintained castration levels of testosterone to Week 49 when treatment stopped compared to 89% of men who received leuprolide. These results showed that relugolix was superior to leuprolide in achieving castration levels of testosterone.

Researchers also measured prostate specific antigen response which is a measure of how well the treatment is working. If prostate specific antigen levels were less than half of what they were before treatment started this was referred to as a PSA response. Prostate specific antigen was lowered more quickly in the relugolix group compared with the leuprolide group, in which an initial increase was seen. However, after 3 weeks of treatment, the prostate specific antigen levels in both groups had decreased and continued to be suppressed throughout the study.

A smaller group of 184 men, who did not need further hormonal treatment at that time, were monitored for an extra 90 days after completing 48 weeks of treatment. After those 90 days, blood testosterone levels had recovered to normal levels in 54% of men taking relugolix compared to only 3% of men receiving leuprolide.

Study C27003
Radiotherapy with androgen deprivation therapy is an established treatment option for patients with intermediate and high-risk prostate cancer. In this study researchers wanted to see how effective relugolix was against the more established GnRH antagonist, degarelix. As expected, the time to castration levels of testosterone was rapid in both groups (4 days in the relugolix group and 3 days in the degarelix group) as both medicines are identical in how they work. Over the treatment period (24 weeks) 95% of men treated with relugolix and 89% of men treated with degarelix had sustained castration levels of testosterone. Similar to the findings in the HERO study, once relugolix treatment had stopped, testosterone levels recovered rapidly within 12 weeks (in 52% of patients). This is in contrast to the degarelix group with only 16% of patients achieving testosterone recovery.

The study also measured prostate specific antigen response to see how well the treatments worked. Prostate specific antigen levels were measured at 12 weeks after treatment had started and at the end of the treatment period (24 weeks). By week 12, halfway through the treatment period, prostate specific antigen was halved in 97% of patients in both groups, and the reduction in prostate specific antigen by 90% was 55% and 47% in the relugolix and degarelix groups, respectively. Prostate specific antigen levels remained low after treatment was stopped with both relugolix (95%) and degarelix (92%), to a similar extent.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:
HERO study

EORTC-QLQ-PR25: The scores for hormonal treatment-related symptoms at the 90 day follow up visit in the relugolix group was lower compared to the leuprolide group, indicating less severity of treatment-related symptoms with relugolix. However, there was no significant improvement in either sexual activity or sexual functioning (in either group) once treatment had stopped. A possible explanation for the lack of improvement is the age of patients (mean age = 72 years) and the small number of patients who responded to the questionnaire. All other measurements completed in the assessment (urinary symptoms, incontinence aid use, and bowel symptoms) were similar between the two groups.

EQ-5D-5L was also used to measure quality of life in the HERO study but there were no expected differences between the two treatment groups because the questionnaire does not measure prostate cancer-specific quality of life impact.

C27003 study

Global health status, as assessed by ***EORTC-QLQ-C30***, and sexual activity and hormonal treatment-related symptoms, as assessed by the ***EORTC-QLQ-PR25***, were worse during treatment in patients on both relugolix and degarelix. Within 12 weeks after treatment stopped, sexual activity scores improved by a mean of 12.1 for relugolix and 6.6 for degarelix (median 8.3 and 0.0, respectively) and hormonal treatment-related symptoms changed by a mean of –5.0 and –1.2 (median -5.6 and 0.0), respectively. Similarly, sexual, psychological scores worsened during treatment in both groups. After treatment stopped, the fast testosterone recovery with relugolix was associated with a rapid improvement in a range of castration-related symptoms on quality of life measures.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

HERO study

The overall incidence of side effects was similar in patients receiving relugolix and leuprolide. A side-effect is any unwanted medical event that happens while a person is taking a medication and may be considered related to (caused by) or unrelated to the medication. Side effects were rated as mild, moderate, or serious. Almost all men experienced some side effects (578 patients or (92.9%) in the relugolix group and 288 patients (93.5%) in the leuprolide group). Most side effects were rated as mild or moderate. Hot flash was the most common side effect in both groups (54.3% in the relugolix group and 51.6% in the leuprolide group). Diarrhoea was reported in a higher percentage of patients in the relugolix group (12.2%) than in the leuprolide group (6.8%). All cases of diarrhoea were mild or moderate and no patient was withdrawn because of diarrhoea. Fatal events (resulting in death) were reported for 1.1% of the patients in the relugolix group and 2.9% of those in the leuprolide group.

Heart attacks, strokes, and deaths due to any cause during the HERO study were recorded as a major adverse cardiovascular event (or MACE for short). The risk of MACE among men taking part in the study was of particular interest because heart attacks and stroke are a major cause of death

among men with prostate cancer and GnRH agonists, such as leuprolide have been linked to an increased chance of heart attacks and stroke. The percentage of men who had a MACE after 48 weeks of receiving leuprolide was double that of men taking relugolix (3% [18 out of 622 men] taking relugolix and 6% [19 out of 308 men] receiving leuprolide). The percentage of men with a previous major adverse cardiovascular event and who had a MACE after 48 weeks of receiving leuprolide was four and a half times that of men taking relugolix (4% [3 out of 84 men] taking relugolix and 18% [8 out of 45 men] receiving leuprolide).

Study C27003
At least one side effect was reported by most patients in both groups (86% in patients taking relugolix , and 97% in patients receiving degarelix), although severe side effects were infrequent (relugolix 2%; degarelix 11%). The most common side effect in both groups was hot flush (relugolix 57%; degarelix 61%). With the exception of injection-site reactions (11%) in the degarelix group, the overall side effect profile was similar between relugolix and degarelix and no patients in either group discontinued treatment due to side effects.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

- Relugolix is a convenient once daily, oral treatment option, which eliminates the need for nurse administration and associated costs, stress and pain of injections.
- There is no initial increase in testosterone levels, eliminating the need for extra treatments, which reduces the burden on patients.
- Relugolix has the unique advantage of being an oral treatment with fast recovery in testosterone levels to normal once off treatment. This is particularly beneficial for men receiving a short course of androgen deprivation therapy (as is commonly administered with radiation therapy) or those wanting to recover from a side effect of treatment.
- Relugolix is associated with a lower risk of cardiovascular events, particularly in men with pre-existing cardiovascular disease (conditions affecting the heart or vessels).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

- The impact of relugolix on survival or disease progression is still unknown. The HERO trial did not provide robust data to determine the risks of prostate cancer related deaths.
- Proving the benefits of relugolix on major adverse cardiovascular events was not the main aim of the HERO study. A recent study, PRONOUNCE, compared a GnRH agonist

(leuprolide) with a GnRH antagonist (degarelix), and found no difference in cardiovascular events [16]. However, there were problems with the PRONOUNCE study and further trials are required to understand if GnRH agonists increase the risk of major adverse cardiovascular events, particularly in men with preexisting cardiovascular disease.

- Although evidence from clinical trials is available, studies looking at compliance (e.g. whether a patient follows medical advice on when to take their treatment) with relugolix in the real-world are limited and additional research is required around predictors of compliance and the consequences of missed doses.
- There is currently limited data on the use of relugolix in combination with agents, such as docetaxel or enzalutamide which are used to treat metastatic prostate cancer. The results of a small study (in 12 patients with high-risk prostate cancer) found that relugolix in combination with apalutamide was effective at maintaining castrate testosterone levels without new safety signals [14] .

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

- The structure of the model captures whether individuals with Hormone Sensitive Prostate Cancer (HSPC) are either on or off androgen deprivation therapy (ADT), whether they remain hormone sensitive or develop resistance and whether their testosterone levels are above or below castrate levels. One very important element in relation to ADTs is the risk of major adverse cardiovascular events (MACE), which may differ by ADT, and which is captured by the model. Lastly, the model captures prostate cancer and MACE-related mortality. This modelling approach in summary adequately represents the natural progression of prostate cancer over time as well as any major adverse events of treatment.
- Relugolix (a GnRH antagonist) reduces the risk of events related to MACE that can happen when taking other types of ADTs known as GnRH agonists, including leuprolide, goserelin and triptorelin. 27% of events related to major adverse cardiovascular events are fatal. Therefore, using relugolix instead of leuprolide or other GnRH agonists, leads to less mortality associated with major adverse cardiovascular events in the model. Data from

the HERO trial suggests that the risk of major adverse cardiovascular events is 62% lower in patients receiving relugolix versus leuprolide.

- The HERO trial data was used in the economic model and informs the probability that patients in the model experience certain outcomes such as sustained castration rate and time to PSA progression. The incidence of major adverse cardiovascular events for relugolix and GnRH agonists was taken from the HERO trial data. The likelihood (probability) of prostate specific antigen progression in the long-term (e.g. over the complete time horizon of the model) was estimated using the HERO trial data. Lastly, the probability of reaching castration levels of testosterone was also based on the HERO trial data.
- Quality of life data was captured in the HERO trial using the EQ-5D questionnaire. These responses were converted to 'utility' values, which measure quality of life on a scale from 0 (death) to perfect health (1). Utilities differed based on whether individuals were on or off treatment, metastatic and whether they were castrate resistant. Disutilities (the reduction in utility as a value of quality of life) related to MACE were also applied which are based on non-fatal events which reduce quality of life.
- Relugolix is given as an oral tablet, compared to other ADTs which are given subcutaneously. This reduces the need for administration by clinical staff and its associated costs.
- The largest uncertainty in the model was associated with the relative risk of major adverse cardiovascular events.
- No additional cases were made in order to take into account severity modifiers which are likely to be relevant to the condition.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:
Relugolix offers patients an option for a treatment that can be taken by mouth at home, as opposed to visiting clinics for regular injections with other androgen deprivation therapies.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:
Accord is not aware of any equality considerations related to relugolix.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

Information on relugolix

- MHRA marketing authorisation for relugolix: https://mhraproducts4853.blob.core.windows.net/docs/14cac18aebcf435b6e6b288b157528c688adf114
- MHRA patient information leaflet for relugolix: https://mhraproducts4853.blob.core.windows.net/docs/9a461baa0e2248397902be06c07adc358f85f637
- Plain language summary of the HERO trial for relugolix: https://www.futuremedicine.com/doi/10.2217/fon-2022-0172

Information on prostate cancer

- Prostate Cancer UK: https://prostatecanceruk.org/
- NICE impact prostate cancer: https://www.nice.org.uk/about/what-we-do/into-practice/measuring-the-use-of-nice-guidance/impact-of-our-guidance/nice-impact-prostate-cancer

4b) Glossary of terms

Response:

Adjuvant/neo adjuvant: Adjuvant **r**efers to a treatment given after the main treatment to reduce the chance of cancer coming back. Neoadjuvant therapy refers to any treatment that is given for cancer before the main treatment with the goal of making the main treatment more likely to succeed.

Advanced prostate cancer: When prostate cancer spreads beyond the prostate or is at high risk of progression or returns after initial treatment, it is called advanced prostate cancer.

Androgens: Androgens are the group of sex hormones that give men their 'male' characteristics. The major sex hormone in men is testosterone.

Androgen deprivation therapy (ADT): A type of hormone therapy used to treat prostate cancer by lowering the levels of androgens, such as testosterone.

Biochemical relapse: Refers to the rise in prostate specific antigen levels in the blood of prostate cancer patients after treatment. It may mean the cancer has come back.

Biopsy: A procedure to remove a piece of tissue or a sample of cells from your body so that it can be examined under a microscope. This can help diagnose a cancer and grade its severity.

Cambridge Prognostic group (CPG): risk groups for prostate cancer which helps determine if you need treatment and the type of treatment you need.

Computerised tomography (CT): A diagnostic imaging test that uses x rays to take detailed pictures of your body.

Disutility: the reduction in utility (see below) as a value of quality of life

dl: decilitre, a metric unit of capacity equal to one tenth of a litre

Genitourinary: urinary and genital organs

Gonadotrophin-releasing hormone (GnRH): A hormone produced by the brain. GnRH instructs the brain to produce luteinizing hormone (LH) which then tells the testicles to make testosterone.

GnRH agonists, antagonists: Types of hormone therapies that act to lower levels of testosterone in the body.

Gleason score: a commonly used grading system for prostate cancer.

Hormone Sensitive Prostate Cancer: Prostate cancer that can be controlled by treatments that lower the levels of testosterone.

Locally advanced prostate cancer: cancer that has started to break out of the prostate or has spread to the area just outside the prostate.

Localised prostate cancer: cancer that is inside the prostate and hasn't spread to other parts of the body.

Luteinizing hormone (LH): A hormone produced by the brain that tells the testicles to make testosterone.

Magnetic resonance imaging (MRI): A type of diagnostic scan that uses magnetism and radio waves to take images of inside the body.

Major adverse cardiovascular events (MACE): Heart attacks, strokes, and deaths due to any cause during the HERO study were recorded as a major adverse cardiovascular event (or MACE for short)

Metastatic prostate cancer: cancer that has spread from the prostate to other parts of the body.

ml: millilitre, a metric unit of capacity equal to one thousandth of a litre

ng: nanogram, a unit of measurement which indicates a mass equal to one thousand-millionth of a gram

Positron emission tomography (PET): A type of imagine procedure that measures the metabolic activity of the cells in your body.

Profound castration: Blood testosterone levels that fall below 20 ng/dl.

Prostatectomy A surgical procedure to remove part of all the prostate**.** A radical prostatectomy is removal of all the prostate.

Prostate specific antigen (PSA): a protein that is secreted by the prostate gland and is used in the diagnosis of prostate cancer.

PSA response: In the HERO trial, If prostate specific antigen levels were less than half of what they were before treatment started this was referred to as a PSA response.
PSA progression: The Prostate Cancer Clinical Trials Working Group 3 (PCWG3) has defined PSA progression as an increase in PSA greater than 25% and >2 ng/ml above its lowest point, confirmed by progression at 2 timepoints at least 3 weeks apart.
Radiotherapy: A treatment using ionizing radiation, usually provided as part of cancer therapy, to kill or control the growth of malignant cells.
Sustained castration: A blood testosterone level below 50 ng/dl that is sustained throughout a treatment period. In the HERO trial testosterone levels were measured from Day 29 through 48 weeks of treatment.
Time horizon: The duration of time over which health outcomes and costs are calculated.
T stage: T refers to size of a cancer and how far it has spread
Utility: A 'utility' in health economics is the measure of the value that an individual or society gives a particular health state. A value of 0 representing death, and a value of 1 representing perfect health

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. Hamdy, F.C., et al., *Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer.* N Engl J Med, 2023. **388**(17): p. 1547-1558.
2. Steele, C.B., et al., *Prostate cancer survival in the United States by race and stage (2001-2009): findings from the CONCORD-2 study.* Cancer, 2017. **123**: p. 5160-5177.
3. National Institute for, H. and E. Care. *Prostate cancer: diagnosis and management (NG131)*. 2019; Available from: https://www.nice.org.uk/guidance/ng131.
4. National Institute for, H. and E. Care. *Degarelix for treating advanced hormone-dependent prostate cancer (TA404)*. 2016 [Available at: https://www.nice.org.uk/guidance/ta404; Accessed on January 3, 2021].
5. FDA, U. *FDA drug safety communication: Update to ongoing safety review of GnRH agonists and notification to manufacturers of GnRH agonists to add new safety information to labeling regarding increased risk of diabetes and certain cardiovascular diseases* 2010 [cited 2023; Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-update-ongoing-safety-review-gnrh-agonists-and-notification.
6. Levine, G.N., et al., *Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology.* Circulation, 2010. **121**(6): p. 833-840.
7. Sciarra, A., et al., *A meta-analysis and systematic review of randomized controlled trials with degarelix versus gonadotropin-releasing hormone agonists for advanced prostate cancer.* Medicine, 2016. **95**(27).
8. Doehn, C., M. Sommerauer, and D. Jocham, *Degarelix for prostate cancer.* Expert Opinion on Investigational Drugs, 2009. **18**(6): p. 851-860.
9. European Medicines Compendium. *Prostap 3 DCS*. Available from: https://www.medicines.org.uk/emc/product/4651/smpc#gref.
10. European Medicines Compendium. *Zoladex LA 10.8mg*. Available from: https://www.medicines.org.uk/emc/product/1567/smpc#gref.

11. European Medicines Agency. *Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data . INN: leuprorelin-containing depot medicinal products*. 2020; Available from: https://www.ema.europa.eu/en/documents/referral/leuprorelin-containing-depot-medicines-article-31-referral-public-assessment-report-prac_en.pdf.
12. Shore, N.D., et al., *Oral relugolix for androgen-deprivation therapy in advanced prostate cancer.* New England Journal of Medicine, 2020. **382(23)**: p. 2187-2196.
13. Dearnaley, D.P., et al., *The Oral Gonadotropin-releasing Hormone Receptor Antagonist Relugolix as Neoadjuvant/Adjuvant Androgen Deprivation Therapy to External Beam Radiotherapy in Patients with Localised Intermediate-risk Prostate Cancer: A Randomised, Open-label, Parallel-group Phase 2 Trial.* European Urology, 2020. **78**(2): p. 184-192.
14. Brown, G., et al., *Coadministration of Apalutamide and Relugolix in Patients with Localized Prostate Cancer at High Risk for Metastases.* Target Oncol, 2023. **18**(1): p. 95-103.
15. De La Cerda, J., et al., *A Phase I Clinical Trial Evaluating the Safety and Dosing of Relugolix with Novel Hormonal Therapy for the Treatment of Advanced Prostate Cancer.* Target Oncol, 2023. **18**(3): p. 383-390.
16. Lopes, R.D., et al., *Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: the primary results of the PRONOUNCE randomized trial.* Circulation, 2021. **144**(16): p. 1295-1307.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Clarification questions

February 2024

File name	Version	Contains confidential information	Date
ID6187 Relugolix 1a. Clarification responses_23.02.24 [CON]	1	Yes	23 February 2024

Section A: Clarification on effectiveness data

Definition of advanced prostate cancer

A1. Could the company please clarify its definition of advanced localised disease in CS B.1.3.2. The description of advanced prostate cancer given in CS B.1.3.2 includes advanced localised disease and states this is “defined as T1 or T2 and PSA between 10 - 20ng/ml and Gleason 3+4 or Gleason grade 4+3”. The reference cited for this description is “Moul JW. The evolving definition of advanced prostate cancer. Reviews in urology. 2004;6(Suppl 8):S10.” However, this reference states that “Patients categorized as having “high risk” localized disease (Table 1) have PSA levels above 20 ng/mL or a Gleason score ≥8, or the 1992 American Joint Committee on Cancer tumor stage T2c or T3. These patients, particularly the younger men, could now be defined as advanced prostate cancer patients because of their increased risk for death from the disease, even though it is detected at a localized stage.”, which is in line with NG131**.**

The original submission had a typographical error in the section referred to by the EAG above. The suggestion from the EAG is correct, and as per the reference and NG131, the text should read:

“The definition has been expanded to encompass patients with significant risk of disease progression and/or death, using stage, Gleason grade and PSA level e.g.

- locally advanced disease (stages T3-T4) and
- advanced localised disease (defined as PSA above 20ng/ml and Gleason score ≥ 8).”

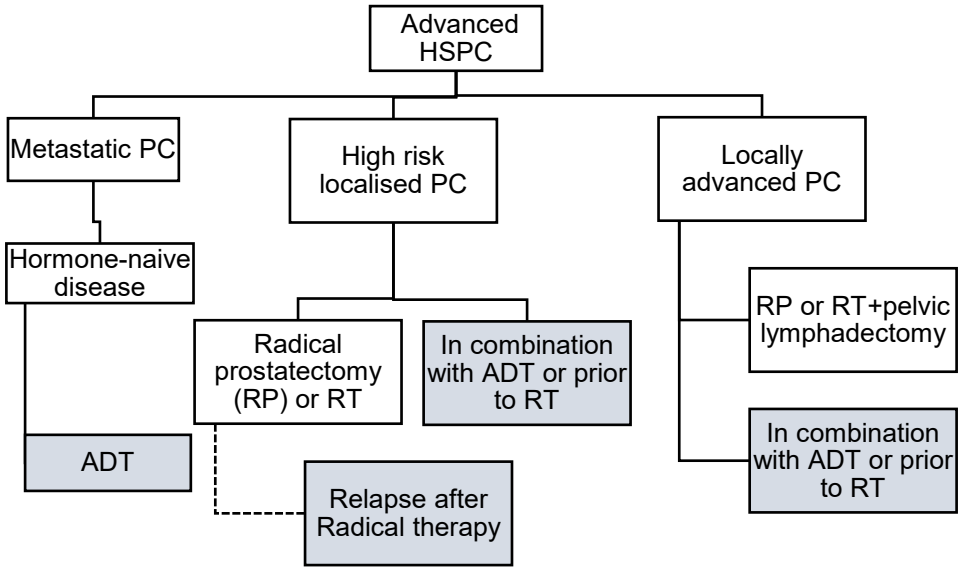
However, NICE guidelines use the Cambridge Prognostic Group (CPG) score to risk stratify patients with prostate cancer. Recommendations within the guidelines suggest to "Offer people with CPG 2, 3, 4 and 5 localised or locally advanced prostate cancer 6 months of androgen deprivation therapy before, during or after radical external beam radiotherapy", and "Consider continuing androgen deprivation therapy for up to 3 years for people with CPG 4 and 5 localised or locally advanced prostate cancer, and discuss the benefits and risks of this option with them". CPG

stage 2 locally advanced within the NICE guidelines is aligned with our company submission definition (Gleason score 3 + 4 = 7 (grade group 2) or PSA 10 microgram/litre to 20 microgram/litre and Stages T1–T2).

A2. Please clarify the interpretation of Figure 1 *'NICE pathway for the management of advanced HSPC prostate cancer'*. Specifically, the position of relugolix as a neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer (one of the subgroups covered by the recent licence variation) is unclear. The blue boxes in the figure say "in combination with ADT" which we assume relates to another group covered by the recent licence variation. Should we assume these blue boxes are also inclusive of neoadjuvant treatment?

Figure 1 in the original submission was intended to reflect the current NICE pathway. The blue boxes should include both adjuvant and neoadjuvant treatment. In order to clarify all the possible positions for relugolix, Accord have redrawn Figure 1 with the wording updated, below.

Figure 1. NICE pathway for the management of advanced hormone-sensitive prostate cancer



Relugolix is indicated (highlighted in blue) for patients with high-risk localised, locally advanced, metastatic hormone-sensitive disease who would otherwise have ADT. Relugolix is also indicated for patients who relapse after radical treatment (broken line). Adapted from NICE treatment recommendations for advanced prostate cancer (NG131) (51) and ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (52).

HSPC = Hormone-sensitive prostate cancer, ADT = androgen deprivation therapy, RP = radical prostatectomy, RT = radiotherapy

Systematic literature review processes

A3. CS Appendix D1.1, study selection (p28) states "*Two reviewers worked independently to screen records and extract data…….full texts of studies meeting inclusion criteria at this stage were included in the review and progressed to data extraction, critical appraisal and ITC feasibility assessment*." Please could the company clarify:

1. How was study selection carried out (e.g. two reviewers each independently screening all records)?

2. How was data extraction carried out (e.g. one reviewer extracting data and a second reviewer checking data extraction)?

3. How was critical appraisal carried out (e.g. one reviewer performing critical appraisal and a second reviewer checking the appraisal)?

1. Each reviewer screened all records independently, with any disagreements or discrepancies between selection resolved through discussion and agreement between the reviewers. If, after discussion between these two reviewers, a consensus was not reached, a third reviewer was consulted to reach consensus.

2. Data extraction was carried out by two reviewers (extracting separate records), with the extraction checked by a third reviewer.

3. Critical appraisal was performed by one reviewer, with a second reviewer checking the appraisal.

A4. In relation to CS Appendix D 1.3: Critical appraisal for each study

- For each study listed in Figure 28 and 29, could the company provide its reasons for the judgements for each domain of Cochrane Collaboration's Risk of Bias tool 2.0

- Could the company please confirm if the unique ID of H00001 in Figure 28 is referring to NCT02083185.

The full reasons for judgements in each domain of the Risk of Bias tool have been provided in an accompanying spreadsheet (Filename:ID6187_RoB assessment) due to the size of the table.

We can confirm that the unique ID of H00001 corresponds to Ctgov 2018 (also known as NCT02083185).

Clinical study reports and related documents

A5. PRIORITY QUESTION Could the company please provide the EAG with the following:

- Protocol for the HERO study
- Statistical Analysis Plan for the HERO study
- The following for the final analysis CSR:
    - All tables, figures and graphs listed in section 7 (“TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT”)
    - Listing 16.2.6.3 (global health status and functional scales in EORTC QLQ-C30)
    - Listing 16.2.6.4 (symptom scales in EORTC QLQ-C30)
    - Listing 16.2.6.5 (EORTC QLQ-PR25)
    - Listing 16.2.6.6 (EQ-5D-5L) (EM)

Accord has obtained and uploaded the following folders and files to NICE Docs:

- HERO_final analysis_CSR [Data on file]
- HERO_SAP [Data on file]
- HERO_Protocol [Data on file]
- Listing 16.2.6.3 [Data on file]
- Listing 16.2.6.4 [Data on file]

- Listing 16.2.6.5 [Data on file]
- Listing 16.2.6.6 [Data on file]
- Tables, Figures and Graphs from Section 7 [Data on file]
    - Accord have not been able to obtain the following from the originator: Figure 7.2.7.11. Figure 7.2.7.12, Table 7.2.9.1.1, Table 7.2.9.12, Table 7.2.11.1, Table 7.3.992, table 7.3.9.18, Table 7.3.10.2.2, and Table 7.3.10.3.2

These files should remain confidential (as data on file).

A6. PRIORITY QUESTION For study NCT02083185 and NCT02135445 could the company please provide the following documents:

- Clinical Study Report
- Protocol
- Statistical Analysis Plan (SAP)

Accord has obtained and uploaded the following folders and files to NICE Docs:

- Folder 1: NCT02083185
    - NCT02083185 (C27002)_CSR [Data on file]
    - NCT02083185 (C27002)_PROTOCOL [Data on file]
    - NCT02083185 (C27002)_SAP [Data on file]
- Folder 2: NCT02135445
    - NCT02135445 (C27003)_CSR [Data on file]
    - NCT02135445 (C27003)_PROTOCOL [Data on file]
    - NCT02135445 (C27003)_SAP [Data on file]

These files should remain confidential (as data on file).

References for CTgov 2018 / NCT02083185

A7. For study, CTgov 2018 / NCT02083185, CS B.2.2.1 (p31) two references are cited for this study:

> 54. Shore ND, Bailen JL, Pieczonka C, Saltzstein DR, Sieber PR, MacLean DB, et al. PD28-01 testosterone lowering, PSA response and quality of life in patients with advanced hormone sensitive prostate cancer receiving TAK-385, an oral GnRH antagonist: phase 2 interim analysis. The Journal of Urology. 2016;195(4S):e654-e.
>
> 55. Saad F, Bailen JL, Pieczonka CM, Saltzstein DR, Sieber PR, Maclean DB, et al. Second interim analysis (IA2) results from a phase II trial of TAK-385, an oral GnRH antagonist, in prostate cancer patients (pts). American Society of Clinical Oncology; 2016.

These references, however, are not stated in CS Appendix D1.1. Table 69 under the "publications" column. Please could the company confirm whether these 2 references were identified in the SLR.

The two references stated were not identified in the SLR. The reason for the exclusion of each reference is outlined below.

54. Shore et al, 2016

This study was not identified for screening as this record was removed by the cited SIGN study design search strategy filter that excluded conference abstract publication types (Line 42 from Embase search strategy). However, even if screened during the abstract screening phase, this record would have been excluded for reason of a conference abstract older than 2018 (as per the SLR protocol, which has been provided [Data on file: MYO32945_Relugolix PC SLR_Study Protocol 2.0 (original SLR)]).

55. Saad et al, 2016

This record was identified during the literature search and excluded during the abstract screening phase for reason of a conference abstract older than 2018. The original SLR protocol stated that only conference proceedings within the past 2 years

of the search date (i.e. March 2020) will be reviewed for inclusion, and this record fell outside of the 2018-2020 timeframe. Given this record was excluded at the abstract screening phase, this record would not have shown up in the excluded publications study listing, which only detail records eligible for full text screening.

In addition to the original protocol for the SLR, Accord have also uploaded the protocol for the subsequent SLR updates [Data on file: Relugolix SLR Updates Protocol (RCT+OLE)_18.04.2023].

Study NCT05605964

A8. Could the company confirm whether study NCT05605964 is included in the evidence submission? This study is listed in the decision problem form as one of three relevant trials to be included in the evidence submission. However, it does not appear in CS Document B or CS Appendix D.

NCT05605964 (also known as REPLACE-CV) was not included in the evidence submission as we had limited information regarding this study. It is not sponsored by Accord, and we have no involvement. Originally, the company had planned to include this, however, given the lack of information we had at the time of submission (i.e. only information that was available on the clinical trials website [https://clinicaltrials.gov/study/NCT05605964?term=replace%20cv&rank=1]), it was decided that it would not add any beneficial detail to the evidence submission.

On receiving clarification questions, Accord reached out to Sumitomo Pharma (previously Myovant), who in turn have given an update.

[redacted]

[redacted]

Study NCT02083185

A9. (see also question A10) Could the company please explain why NCT02083185 is not given the same weight as HERO and NCT02135445 in the evidence submission and is excluded from the NMA. In the decision problem form the company listed NCT02083185, a phase II study, as one of three relevant trials to be included in the submission. Although this study is one of the included studies in the systematic literature review (CS Appendix D Table 69), CS Appendix D page 50 states this study "*was not used to populate the economic model, and is not included in the following section of this submission as the evidence has been superseded by the results of the HERO trial*". Furthermore, it does not appear in the NMA, despite having potentially relevant results (see https://classic.clinicaltrials.gov/ct2/show/results/NCT02083185?view=results). This study does meet the exclusion criteria of the NMA (CS Appendix D Table 72) in that *"Phase II RCTs were excluded if a Phase III RCT that evaluated the same intervention and comparator(s) was included*" (CS Appendix D Table 72). However, excluding a study purely because it is a phase II study appears inappropriate, particularly if the evidence could provide greater certainty in the assessment of the clinical effectiveness of relugolix.

Although NCT02083185 was listed as a relevant study in the Decision Problem meeting, there are a number of reasons why Accord chose to provide only a summary in the full submission (in section D1.1 of the submission made on 24th January, as this information was moved to the appendices following a request to shorten the main body of document B).

First, NCT02083185 has not been published in full, and has only been published as conference abstracts (Saad et al 2016, Shore et al 2016, as per the response to question A7). This study was sponsored by Takeda, and subsequently relugolix was licensed to Myovant (now Sumitomo Pharma), before being licensed by Accord. Therefore, access to the full dataset was limited at the time of submission (and has been provided to Accord once context regarding the clarification questions was given).

Further, as mentioned in the submission, NCT02083185 was not used to populate the economic model, and as per the NICE user guide, “Sections 2.2 to 2.6 of the submission should include only the trials that were included in the economic model.”. Accord does not believe that NCT02083185 provides any additional support for the use of relugolix beyond the evidence given in the HERO trial, since both trials assess relugolix against the same comparator (leuprolide) in the same patient population. The phase 3 HERO trial was deemed to provide much more robust data in a larger population.

Due to reasons above, as well as the lack of power to support a statistical comparison between interventions, NCT02083185 was originally not included in the NMA. The EAG has requested a scenario where this is included in question A11.

Indirect treatment comparisons

A10. Please provide the WinBUGS code used for the NMA.

The WinBUGS code used for both of the NMAs is included in the full NMA report [Data on file] which has been uploaded to NICE Docs as part of our response. Accord have also uploaded a standalone document [Data on file: NMA WinBUGS Code] only containing the code (as it was used in response to question A11).

A11. PRIORITY QUESTION (see also question A8) Please include the phase 2 study NCT02083185 in the NMA. We do not consider study phase a justifiable exclusion criterion.

At the request of the EAG, the NMA for testosterone suppression has been rerun with the data from NCT02083185 included. Since NCT02083185 did not report MACE outcomes, it was not feasible to include it in the NMA of Major CV-related events (MACE).

The results of the updated NMA for testosterone suppression to castrate levels (<50ng/dL) are as follows. Raw data on testosterone suppression to castrate levels (<50ng/dL) from RCTs of treatment for HSPC are summarised in Table 1.

Table 1. Individual study data for testosterone suppression

Study Name	Treatment Name

	Relugolix		Degarelix		Triptorelin		Goserelin		Leuprolide 3M		Leuprolide 1M	
	n	N	n	N	n	N	n	N	n	N	n	N
HERO (38)	601	622							274	308		
CS21 (60)			202	207					194	201		
CTGov 2018	100	110							23	24		
Heyns 2003 (69)					130	132			135	139		
Tanaka 2007 (73)							11	11			10	11
Silva 2012 (72)							13	20	15	20	14	20

Estimated treatment effects expressed as odds ratios (ORs) and relative risks (RRs) are presented in Table 2 and Table 3(with degarelix) and Table 4 and Table 5(without degarelix) for the best-fitting model: random effects hierarchical NMA with informed priors. There were no statistically significant differences between relugolix and other ADTs, as the 95% confidence interval for these ORs contained the value 1.0. This is likely due to the inclusion of the phase 2 study (NCT02083185), which did not aim to assess formal statistical differences either between the two relugolix doses, or between relugolix and leuprolide.

Table 2. League table for odds ratios of testosterone suppression to castrate levels: Primary analysis including degarelix

Relugolix			
1.03 (0.48 - 3.59)	**Degarelix**		
1.50 (0.46 - 6.04)	2.2 (0.28 - 5.99)	**Triptorelin**	
2.04 (0.88 - 4.48)	2.21 (0.61 - 4.95)	1.01 (0.47 - 3.88)	**Leuprolide 3M**

1.88 (0.66 - 8.18)	2.62 (0.47 - 7.68)	1.01 (0.43 - 5.58)	1.18 (0.43 - 2.95)	**Goserelin**	
1.98 (0.71 - 8.40)	2.67 (0.50 - 7.96)	1.05 (0.46 - 6.03)	1.02 (0.33 - 2.16)	1.07 (0.38 - 2.4)	**Leuprolide 1M**

Table 3. League table for relative risks of testosterone suppression to castrate Levels: Primary analysis Including degarelix

Relugolix					
1.01 (0.98 - 1.09)	**Degarelix**				
1.04 (0.98 - 1.17)	1.04 (0.94 - 1.16)	**Triptorelin**			
1.05 (1.00 - 1.12)	1.04 (0.97 - 1.11)	1 (0.92 - 1.07)	**Leuprolide 3M**		
1.06 (0.99 - 1.24)	1.05 (0.96 - 1.22)	1.01 (0.93 - 1.17)	1.01 (0.95 - 1.16)	**Goserelin**	
1.06 (0.99 - 1.25)	1.05 (0.96 - 1.22)	1.01 (0.93 - 1.18)	1.01 (0.96 - 1.16)	1 (0.91 - 1.11)	**Leuprolide 1M**

Table 4. League table for odds ratios of testosterone suppression without degarelix

Relugolix			
1.15 (1.15 - 7.21)	**Triptorelin**		
1.67 (1.67 - 10.2)	1 (1 - 8.36)	**Goserelin**	
2.00 (2.00 - 5.19)	1.01 (1.01 - 5.22)	0.79 (0.79 - 2.57)	**Leuprolide 3M**

1.83 (1.83 - 10.68)	1.06 (1.06 - 8.9)	0.9 (0.9 - 3.07)	0.98 (0.98 - 3.72)	**Leuprolide 1M**

Table 5. League table for relative risks for testosterone suppression without degarelix

Relugolix				
1.05 (1.05 - 1.21)	**Triptorelin**			
1.07 (1.07 - 1.31)	1.02 (1.02 - 1.23)	**Goserelin**		
1.05 (1.05 - 1.15)	1 (1 - 1.08)	0.98 (0.98 - 1.06)	**Leuprolide 3M**	
1.07 (1.07 - 1.33)	1.02 (1.02 - 1.24)	1 (1 - 1.14)	1.02 (1.02 - 1.22)	**Leuprolide 1M**

Although probability of achieving castration is implemented in the cost-effectiveness model, because there is no impact on PSA progression it has no impact on the incremental cost effectiveness ratio (ICER). Therefore, these updated NMA results have no impact on the cost effectiveness analysis.

A12. Did the Margel 2019 study which is included as a MACE / CV endpoint sensitivity analysis also report cumulative probability of testosterone suppression to castrate levels (<50ng/dL). If so, please perform a sensitivity analysis including this study for completeness.

Margel 2019 did not report cumulative probability of testosterone suppression to castrate levels (<50ng/dL). Only data from the <20ng/dL threshold was reported in the manuscript and/or supplementary materials (which have been uploaded to NICE Docs for completeness). Due to the different definition and threshold, it was not considered possible to synthesise the results of Margel 2019 in the NMA of testosterone suppression to castrate levels.

A13. A limited selection of baseline characteristics are reported in Table 75. (Appendix D). Please consider including additional characteristics, including any significant prognostic factors.

The SLR protocol (Data on file, provided in response to question A7) specified patient characteristics as follows: mean age, race/ethnicity and prior treatment. In addition, all pre-specified treatment outcomes were to be extracted at baseline, week 2, 6 months, and/or change (in order to ultimately assess the change in the endpoint). These endpoints included: testosterone suppression to castrate level, PSA response rate, FSH suppression, time to castration resistance, testosterone recovery after discontinuation, overall survival, HRQoL.

The table presented in the company submission presents mean age, mean duration of disease, metastatic disease (as a proportion of the population), and prior hormone therapy.

Other patient characteristics that were extracted (and were not included in the company submission) were race/ethnicity, stage (and classification system from which this was determined), and prior treatment for advanced prostate cancer (surgery, radiation therapy, immunotherapy, adjuvant therapy, other therapy).

Race/ethnicity was not reported in the included SLR citations of the 5 studies of interest. Disease stage was assessed by different methods in each of the 5 studies of interest: Heyns 2003 used the Whitmore-Jewett Classification system; CS21 and Tanaka 2007 used the AJCC classification system, the HERO trial used Gleason Score; and Silva 2012 included only patients who were classed as "Advanced". This information has been provided in Table 6.

Table 6. Summary of baseline cancer stage for studies identified by the SLR

Trial Name	Treatment	N	Cancer Stage Classification system	Stage, % (n/N) per stage
HERO	Leuprolide (LA)	308	Gleason Score	Metastatic: 97, 31.5% 2-4: 0.3% (1/308) 5-6: 14.9% (46/308) 7: 39.6% (122/308) 8-10: 43.5% (134/308) Missing data: 1.6% (5/308)
	Relugolix	622	Gleason Score	Metastatic: 31.8% (198/622) 2-4: 0 5-6: 15.8% (98/622) 7: 38.1% (237/622)

Trial Name	Treatment	N	Cancer Stage Classification system	Stage, % (n/N) per stage
				8-10: 42.9% (267/622) Missing data: 3.2% (20/622)
CS21	Degarelix (240/80mg)	202	AJCC	Localized: 33% (69/207) Locally advanced: 31% (64/207) Metastatic: 18% (37/207) Incompletely classified: 18% (37 (207)
	Degarelix (240/160mg)	207	AJCC	Localized: 29% (59/202) Locally advanced: 31% (62/202) Metastatic: 20% (41/202) Incompletely classified: 20% (40/202)
	LA	201	AJCC	Localized: 31% (63/201) Locally advanced: 26% (52/201) Metastatic: 23% (47/201) Incompletely classified: 19% (39/201)
Heyns 2003	LA	140	Whitmore-Jewett	C: 60.7% D: 39.3%
	Triptorelin	137	Whitmore-Jewett	C: 62.0% D: 38.0%"
Silva 2012	Goserelin	20	--	Advanced
	LA (3.75mg)	19	--	Advanced
	LA (7.5mg)	20	--	Advanced
Tanaka 2007	Goserelin	11	AJCC	All T2-4, Nx, Mx
	LA	11	AJCC	All T2-4, Nx, Mx
	Diethylstilbestrol (DES)	33	--	--
	Goserelin	230	--	--

Information on prior treatment was also sparse and was mostly determined by the inclusion criteria for the studies. For completeness, this data has also been included in Table 7.

Table 7. Summary of prior treatment for advanced prostate cancer for studies identified by the SLR

Trial Name	Treatment	N	Prior treatment for advanced prostate cancer (%, (n/N)						
			Surgery	Radiation therapy	Immunotherapy	HT	Adjuvant	Neoadjuvant	Other
HERO	Leuprolide (LA)	308	--	29.9% (92/308)	--	10%	--	--	--
	Relugolix	622	--	30.5% (190/622)	--	13%	--	--	--
CS21	Degarelix (240/80mg)	202	--	--	--	--	--	--	--
	Degarelix (240/160mg)	207	--	--	--	--	--	--	--
	LA	201	--	--	--	--	--	--	--
Heyns 2003	LA	140	--	--	--	--	--	--	--
	Triptorelin	137	--	--	--	--	--	--	--
	Goserelin	20	--	--	--	--	--	--	--

Trial Name	Treatment	N	Prior treatment for advanced prostate cancer (%, (n/N)						
Silva 2012	LA (3.75mg)	19	--	--	--	--	--	--	--
	LA (7.5mg)	20	--	--	--	--	--	--	--
Tanaka 2007	Goserelin	11	0%	0%	0%	0%	0%	0%	0%
	LA	11	0%	0%	0%	0%	0%	0%	0%
	Diethylstilbestrol (DES)	33	--	--	--	--	--	--	--
	Goserelin	230	--	--	--	--	--	--	--

In terms of outcomes collected at baseline, these data are sparse. Only 1 study (Heyns 2003) reported in table 75 reported a baseline efficacy measure (median PSA concentration per treatment group). Therefore, since no comparisons between studies could be made, this data was not included in the table.

A14. Please summarise the evidence on prognostic factors and treatment effect modifiers in hormone-sensitive prostate cancer.

Literature have identified potential prognostic factors for patients with HSPC, including: age, PSA concentration, WHO performance status, Gleason sum score, whether the patient had been diagnosed with synchronous or metachronous metastatic disease, percentage of biopsy-positive core, T-stage, and N-stage .[1][2]

During the feasibility assessment for the NMA, potential prognostic factors were assessed to determine if their heterogeneity between clinical trials would introduce bias into the NMA.

It was identified that the proportions of patients with distant metastases between trials may introduce bias to the potential ITCs if presence of distant metastases

[1] Shiota M, Terada N, Saito T, Yokomizo A, Kohei N, Goto T, Kawamura S, Hashimoto Y, Takahashi A, Kimura T, Tabata KI, Tomida R, Hashimoto K, Sakurai T, Shimazui T, Sakamoto S, Kamiyama M, Tanaka N, Mitsuzuka K, Kato T, Narita S, Yasumoto H, Teraoka S, Kato M, Osawa T, Nagumo Y, Matsumoto H, Enokida H, Sugiyama T, Kuroiwa K, Inoue T, Mizowaki T, Kamoto T, Kojima T, Kitamura H, Sugimoto M, Nishiyama H, Eto M; Japanese Urological Oncology Group (JUOG). Differential prognostic factors in low- and high-burden de novo metastatic hormone-sensitive prostate cancer patients. Cancer Sci. 2021 Apr;112(4):1524-1533. doi: 10.1111/cas.14722. Epub 2021 Feb 13. PMID: 33159829; PMCID: PMC8019198.

[2] Vale, C. L.; Fisher, D. J.; Godolphin, P. J.; Rydzewska, L. H.; Boher, J.-M.; Burdett, S.; Chen, Y.-H.; Clarke, N. W.; Fizazi, K.; Gravis, G.; James, N. D.; Liu, G.; Matheson, D.; Murphy, L.; Oldroyd, R. E.; Parmar, M. K. B.; Rogozinska, E.; Sfumato, P.; Sweeney, C. J.; Sydes, M. R.; Tombal, B.; White, I. R.; Tierney, J. F. Which Patients with Metastatic Hormone-Sensitive Prostate Cancer Benefit from Docetaxel: A Systematic Review and Meta-Analysis of Individual Participant Data from Randomised Trials. The Lancet Oncology 2023, 24 (7), 783–797.

modifies treatment effects for any of the outcomes of interest. This was highlighted to be of particular concern for the OS endpoint, as patients with non-metastatic disease are likely to have lower mortality risk compared to those with distant metastases.

Additionally, many trials excluded patients with prior hormonal therapy (HT) (including ADT) for advanced HSPC, suggesting that all patients enrolled were treatment-naïve, while 10% (leuprolide) and 13% (relugolix) of patients overall in the HERO trial had prior HT for early disease.

Assessments of clinical heterogeneity during the NMA feasibility assessment did not identify any differences in patient populations between trials contributing to the evidence networks that would be a source of material bias.

The NMA report (Data on file: NMA Report 2023 05 03) and feasibility report (Data on file: NMA Feasibility Assessment 2022 07 26) have been provided as additional material.

A15. Please provide more information on the choice of outcome measures for the NMA.

- Table 72: *'Eligibility Criteria for Studies Contributing to the NMA'* lists outcomes of interest to the NMA, including rates of achieved testosterone suppression, PSA response, overall survival and MACE.

- Table 73: *'Summary of RCTs used to carry out the indirect or mixed treatment comparison'* gives basic details of 5 RCTs, with no mention of outcome measures, despite the accompanying text alluding to differences in outcome definitions and timepoints between trials.

- Later, on page 58, it is stated that *"NMAs assessing the efficacy and safety of treatments for HSPC were feasible for two outcomes: Testosterone suppression to castrate levels (<50ng/dL) and MACE or CV-related events".*

However, no evidence is presented to justify this statement. If sufficient evidence from trials is available please provide NMA results for the other eligible outcomes (as per Table 72), namely PSA response and overall survival. If it is not considered feasible please provide a more transparent explanation to support this.

A full feasibility assessment was undertaken to assess the suitability of all the included SLR citations for synthesis via indirect treatment comparison. The feasibility report and NMA report have been included as additional data on file to supplement the below explanation.

As outlined in the submission, an initial SLR was conducted in March 2020, and was subsequently updated in February 2022 and April 2023. The feasibility assessment for the ITCs was conducted following the first SLR update, according to the criteria outlined in Table 72 and ultimately resulting in the inclusion of the 5 RCTs summarised in Table 73.

There are two discrepancies between the SLR inclusions in the submission and the feasibility report. The first is the inclusion of the PRONOUNCE trial in the feasibility assessment. The results of this study were excluded from the SLR as the population was not deemed to fit the inclusion criteria. However, the protocol for the study was originally included in the first SLR, and therefore the study was assessed for feasibility. However, this does not change the results of the ITC, as the study was not deemed feasible to synthesise. NCT00946920 was also not included in the feasibility report, as it did not have a comparable outcome. The observed outcome of this trial was the proportion of testosterone suppression relative to the administration of degarelix measure as a cumulative probability curve (time to event), which is fundamentally different to the other trials in the NMA, which measure TS as the percentage of patients with TS (providing a single percentage value). It was not possible to extract a percentage value from NCT00946920 as the percentage for degarelix would have to be assumed, and reducing time to event curves would remove too much information, enough that it would not be comparable to HERO or other trials measuring TS as a percentage value.

It is important to clarify that the feasibility report was not updated following the completion of the second update to the SLR. Of the 10 citations that were added, 7 studies were single arm trials (Ctgov 2010/ NCT00117286, Ctgov 2010/ NCT00215683, Ctgov 2010/ NCT00268892, Ctgov 2013/ NCT01215513, Ctgov 2017/ NCT02015871, Ctgov 2017/ NCT02712320, Ctgov 2019/ NCT01964170), which would not facilitate an ITC. Of the remaining 3 studies that were included, Bolla et al 2021 was not a randomised trial, Koontz 2023 was an abstract only with

no results presented, and Tombal 2023 was also abstract only and did not report sufficient information to facilitate an indirect comparison.

The full feasibility report has been provided alongside this response, however, a summary for each outcome of interest presented in Table 72 is provided below.

Rates of achieved TS (testosterone <50 ng/dL), referred to as testosterone suppression to castrate levels

Information on testosterone suppression was available from 12 unique trials (Table 8). Ten trials defined testosterone suppression as testosterone levels <50 ng/dL, whilst the remaining two employed a threshold of 100 ng/dL. There was also considerable heterogeneity in terms of the timepoints at which the outcome was assessed. For the 10 trials that implemented a consistent threshold for testosterone suppression, it may have been feasible to conduct an ITC, however any potential ITC would be biased if time since treatment initiation modifies treatment effects.

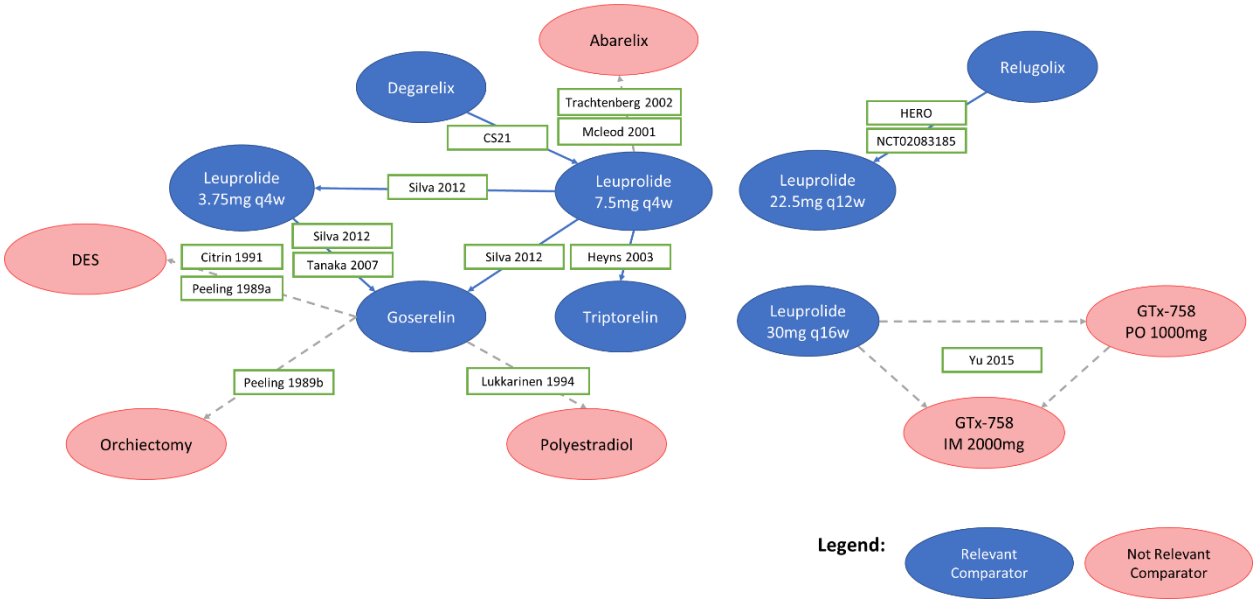
Table 8. Thresholds for Testosterone Castration Rates in Clinical Trials of Medical ADT Identified by the Systematic Literature Review

Author/Year	Study Name	Threshold	Time Point
Bruun 1996	Bruun 1996	100 ng/dL	NR
Klotz 2008	CS21	50 ng/dL	364 days
Citrin 1991	Citrin 1991	50 ng/dL	120 weeks
CTgov 2018	NCT02083185	50 ng/dL	25 weeks
Heyns 2003	Heyns 2003	50 ng/dL	2 months
McLeod 2001	McLeod 2001	50 ng/dL	29 days
Shore 2020	HERO	50 and 20 ng/dL	48 weeks
Silva 2012	Silva 2012	50 ng/dL	3 months
Tanaka 2007	Tanaka 2007	50 ng/dL	28 days

Author/Year	Study Name	Threshold	Time Point
Trachtenberg 2002	Trachtenberg 2002	50 ng/dL	169 days
Yu 2015	Yu 2015	50 ng/dL	60 days
Waymont 1992	Waymont 1992	100 ng/dL (equivalent)	4 weeks

A connected evidence network () was produced, but relugolix was not connected since no head-to-head trials have compared leuprolide 22.5mg Q12W and leuprolide 7.5mg Q4W. However, this assumption was believed to be reasonable since the cumulative dosage received after 3 months of treatment would be equivalent (i.e., 22.5mg). As presented in , a number of the included studies connected relugolix to treatments that were not considered to be relevant comparators in the final NICE scope (marked in red). Therefore, the remaining 5 studies for inclusion were HERO, Heyns 2003, Silva 2012, Tanaka 2007 and CS21 (as per Table 73 in the company submission).

Figure 2. Connected Evidence Network for Potential ITC of Testosterone Suppression Based on Testosterone Levels <50ng/dL



Rates of prostate-specific antigen (PSA) response (≥50% reduction in PSA)

Information on PSA response was identified by the SLR in 5 unique studies (Table 9). There was substantial heterogeneity across trials with respect to the threshold used to define PSA response and the timepoints at which this outcome was assessed. Given this heterogeneity, it was not possible to construct a connected evidence network from relugolix to any of the comparators of interest for PSA response with a threshold of ≥50% reduction in PSA, since the only other study assessing the same threshold as HERO compared leuprolide with abarelix, which was not considered a comparator of interest.

Table 9. Thresholds for PSA Response in Clinical Trials of Medical ADT Identified by the Systematic Literature Review

Author/Year	Study Name	Threshold	Time Point
Autio 2021	Autio 2021	Undetectable PSA	8 months
Tombal 2010	CS21	<4ng/ml	28 days, 364 days
Ctgov 2018	NCT02083185	≥50% and ≥90%	4 weeks
Shore 2020	HERO	≥50%	15 days
Trachtenberg 2002	Trachtenberg 2002	≥50%	169 days

Time to PSA progression (PSA ≥25% and ≥2ng/mL above the nadir)

Information on time to PSA progression was available from 4 trials, including the HERO trial, the CS21 trial, PRIORITI, and the open-label study by Autio (2021). Two trials employed a similar definition for PSA response: HERO and PRIORITI (Xie 2020). Autio 2021 did not report the definition used for PSA progression, and in the CS21 trial, PSA progression was defined as an increase in PSA ≥50% and ≥5ng/mL above the nadir (Table 10).

Table 10. Definitions for PSA Progression in Clinical Trials of Medical ADT Identified by the Systematic Literature Review

Author/Year	Study Name	Definition	Available Information
Data on file	HERO	PSA ≥25% and ≥2ng/mL above the nadir	Kaplan-Meier curve
Xie 2020	PRIORITI	PSA ≥2ng/mL above the nadir	Median (not reached)
Autio 2021	Autio 2021	Not reported	Median
Tombal 2010	CS21	PSA ≥50% and ≥5ng/mL above the nadir	Kaplan-Meier curve

While the HERO and PRIORITI trials evaluated time to PSA progression using a consistent definition, the median time was not reached for the latter and therefore there was no information on the relative effects for therapies in this trial to be used in an ITC. Median time to PSA progression was reported for the Autio 2021 study. However, it is not possible to construct a connected evidence network from Autio 2021 to the HERO study. The definition used for time to PSA progression in CS21 was inconsistent with that employed in HERO. As there is no available evidence on the relative treatment effects on time to PSA progression using a consistent definition in a connected evidence network, an ITC comparing time to PSA progression with medical ADTs was determined to be infeasible.

Overall survival (Kaplan-Meier curves)

Published information on overall survival (OS) was available from 13 clinical trials identified by the SLR and unpublished analyses of OS were available from the CSR of the HERO trial (Table 11). Among the 14 trials, Chodak 1991 and Moffat 1990 reported only median survival times and Heyns 2003 reported only landmark survival at 9 months. Kaplan-Meier curves were available for the remaining 11 trials. None of the 11 trials reported measures of treatment effects expressed as a hazard ratio (HR) for OS, likely due to the short duration of trials. Whilst it would have been

possible to estimate the HR for OS for HERO using patient-level data, the estimated treatment effect would be limited by the immaturity of the data (12 months). For the other 10 trials that reported Kaplan-Meier OS curves, relative treatment effects could be estimated with Cox regression by digitising the curves to recreate pseudo-failure time data. However, none of these trials reported statistically significant differences in survival between treatment arms. For trials that only reported median or landmark survival times, an ITC could be conducted based on the between-group differences in these statistics, but the findings from such an ITC would be of limited evidentiary value.

Table 11. Available Information on OS from Clinical Trials of Medical ADT Identified by the Systematic Literature Review

Author/Year	Study Name	Available Information	Median Follow-Up (months)
Data on file	HERO	Kaplan-Meier survival	12
Tombal 2010	CS21	Kaplan-Meier survival	NR
Bruun 1996	Bruun 1996	Kaplan-Meier survival	NR
Chodak 1991	Chodak 1991	Median survival	17
Citrin 1991	Citrin 1991	Kaplan-Meier survival	22
De Voogt 1998	EORTC GU 30843	Kaplan-Meier survival	68
Garnick 1984	Garnick 1984	Kaplan-Meier survival	12
Heyns 2003	Heyns 2003	Landmark survival at 9 months	9
Huben 1988	NPCTGP 1700	Kaplan-Meier survival	NR
Klioze 1988	Klioze 1988	Kaplan-Meier survival	NR
Moffat 1990	Moffat 1990	Median survival	NR
Peeling 1989a	Peeling 1989a	Kaplan-Meier survival	24
Peeling 1989b	Peeling 1989b	Kaplan-Meier survival	26
Waymont 1992	Waymont 1992	Kaplan-Meier survival	43

MACE

In HERO, MACE was a prespecified safety analysis defined as non-fatal myocardial infarction (MI), non-fatal stroke, ischemic heart disease (IHD), other-non-fatal CV events, and death from any cause. No other trials evaluated MACE as an outcome, however 10 trials did report rates of CV-related events including MI, stroke, IHD, fatal CV-related events, and other non-fatal CV-related events. Other non-fatal CV-related

events varied across trials and included transient ischemic attack, carotid atherosclerosis, angina, peripheral edema, congestive heart failure, thrombosis, pulmonary embolism, tachycardia, and nonspecific CV-related events (i.e., the types of events were not reported).

Table 12. Available Information on CV-Related Events from Clinical Trials of Medical ADT Identified by the Systematic Literature Review

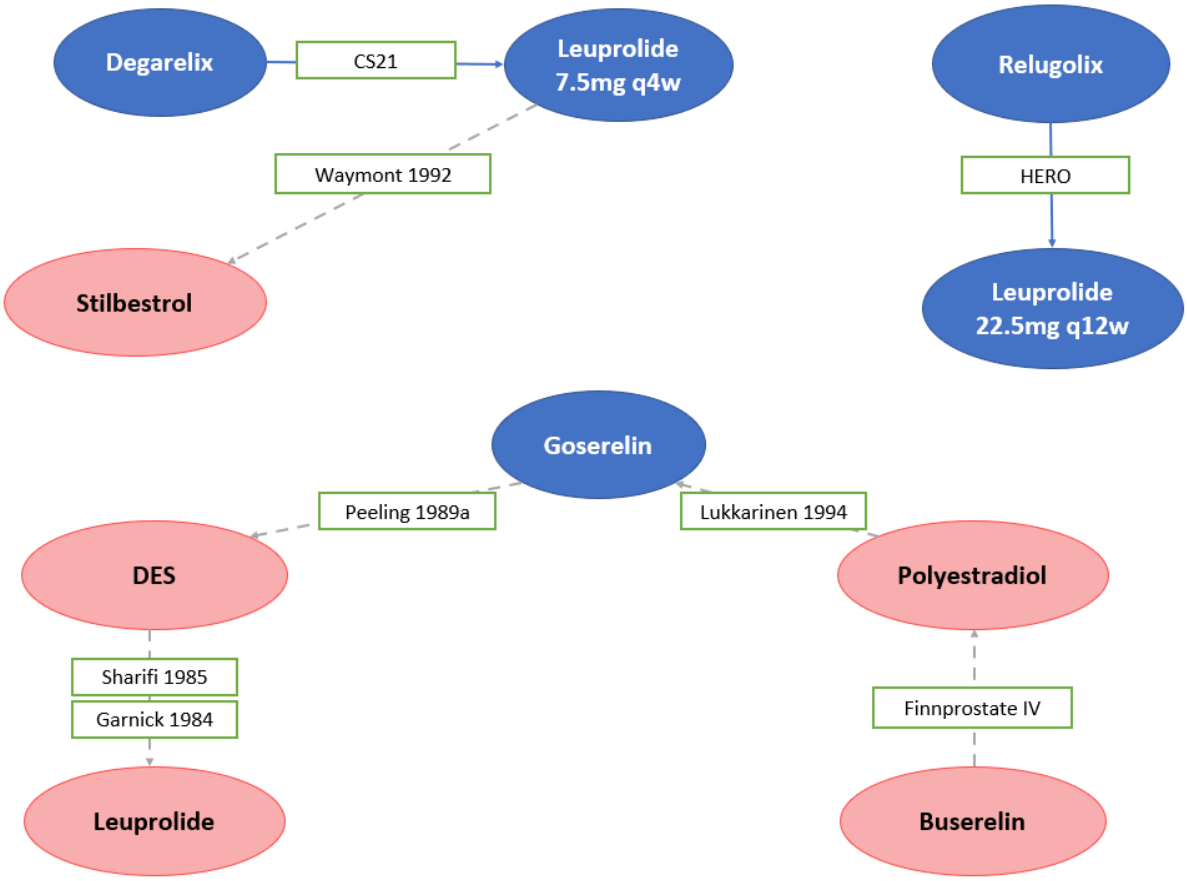
Author/ Year	Study Name	MI	Stroke	IHD	Other Non-Fatal CV Events	Fatal CV-Related Events	Notes
Data on file	HERO	X	X	X	X	X	
Smith 2010	CS21		X	X		X	
Garnick 1984	Garnick 1984	X			X		
Lukkarinen 1994	Lukkarinen 1994					X	
Peeling 1989a	Peeling 1989a					X	
Waymont 1992	Waymont 1992				X		Non-specific CV complications
Aro 1993	Finnprostate IV				X	X	Non-specific CV complications

Author/ Year	Study Name	MI	Stroke	IHD	Other Non-Fatal CV Events	Fatal CV-Related Events	Notes
Sharifi 1985	Sharifi 1985				X		
Yu 2015	Yu 2015	X			X		Only SAEs were reported
Moffat 1990	Moffat 1990				X		Non-specific CV complications

CV: Cardiovascular; MI: Myocardial infarction; IHD: ischemic heart disease; SAE: Serious adverse events

Yu 2015 and Moffat 1990 could not be used to construct connected evidence networks with any other studies. With the remaining 8 studies, three separate networks could be constructed (Figure 3). Although relugolix was not connected to either of the evidence networks, this could be remedied by an assumption leuprolide 7.5 mg q4w and 22.5 mg q12w are equivalent in effects on the outcomes of interest. Goserelin could not be compared against any other comparators of interest. As mentioned in the submission and NMA report, an additional study was identified after the original ITCs were conducted which had previously not been included due to an indexing error (Margel 2019). This was included as an analysis in the company submission.

Figure 3. Connected Evidence Network for Potential ITC of CV-Related Events



Section B: Clarification on cost-effectiveness data

During the process of updating the cost-effectiveness model in response to the clarifications raised, several model amends and corrections have resulted in a new base case result. As such, any scenarios presented in response to clarifications below have been compared to the base case from the updated model, not the version of the model submitted alongside the company submission.

Modelled population and subgroups

B1. Baseline history of MACE. Please clarify the source for the adjustment factor that is used to estimate the proportion of patients with a history of MACE events at baseline (1.241) (CS B.3.2.1) and explain in detail how this value was calculated.

To account for the impact age has on likelihood of prior MACE, an adjustment factor was applied to the initial proportion of patients with history of MACE. This adjustment factor was calculated using the prevalence of prior MACE based on the percentage of patients with cardiovascular (CV) event diagnoses with initiation of ADT in a 12-month lookback period among all patients (combined population) and then stratified by Commercial and Medicare subgroups. The adjustment factor was calculated as the ratio of the prevalence of prior MACE in the Medicare subgroup to the prevalence in the combined population. So, for Medicare (used due to the relative age of the cohort and its similarity to the model's patient population starting age) 21.2% / 17% = 1.241 was the calculated adjustment factor.

Following a review of the Pharmetrics claims data, the use of an age adjustment factor within the model is no longer deemed appropriate given the source used for the proportion of patients with history of MACE (Albertsen et al. 2014). The model population baseline age is 71, which is already aligned to the population in the Albertsen et al (2014) study, 71.6 (range: 51-98). Therefore, the proportion of individuals with prior MACE (30.4%) from the Albertsen et al. study is already deemed reflective of the population presented in the CEM, without the need for any further adjustments.

Therefore, the adjustment factor has been removed from the model's base case and subsequent subgroup and sensitivity analyses.

We have presented a scenario analysis looking at the relatively minor impact on the ICER when excluding the adjustment factor (Table 13):

Table 13. Scenario analysis: exclusion of the age adjustment factor for proportion with prior MACE

Treatment	Adjustment factor (1.241)	Absolute cost (£)	Absolute QALY	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Relugolix	Included	[redacted]	[redacted]			
Blended comparator approach (GnRH agonists)	Included	[redacted]	[redacted]	[redacted]	[redacted]	10,832
Triptorelin (Cheapest GnRH agonist)	Included	[redacted]	[redacted]	[redacted]	[redacted]	11,523
Goserelin (Most expensive GnRH agonist)	Included	[redacted]	[redacted]	[redacted]	[redacted]	10,120
Relugolix	Excluded	[redacted]	[redacted]	-	-	-
Blended comparator approach (GnRH agonists)	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	10,518
Triptorelin (Cheapest GnRH agonist)	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	11,224
Goserelin (Most expensive GnRH agonist)	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	9,791

B2. Base case subgroups. The economic base case analysis includes three subgroups within the broad advanced HSPC population (CS B.3.2.1): patients with locally advanced disease who are not candidates for curative therapy (LA); patients with biochemical relapse following local therapy with curative intent and without metastatic disease (BR); and patients with metastatic disease (mHSPC). Please report cost-effectiveness results separately for these three subgroups.

The pairwise cost effectiveness results are reported in the tables (Table 14-Table 17) below, for relugolix against the blended GnRH agonist comparator, triptorelin (cheapest GnRH agonist) and goserelin (most expensive GnRH agonist) for the wider indication (LA and BR), whilst degarelix is also included as a comparator in the narrower spinal metastases patient group. Please note, due to structural limitations of the model, only three GnRH agonists may be presented at once. As such, the model has been updated to show results for the least expensive GnRH agonist (triptorelin), most expensive (goserelin), and a blended mix of all three GnRH agonists (triptorelin/goserelin/leuprolide):

Table 14. Pairwise cost effectiveness results – base case

Subgroup	Treatment	Absolute cost (£)	Absolute QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
Base case	Relugolix	[redacted]	[redacted]	-	-	-
	Blended GnRH agonist Comparator	[redacted]	[redacted]	[redacted]	[redacted]	10,518
	Triptorelin (Cheapest)	[redacted]	[redacted]	[redacted]	[redacted]	11,224
	Goserelin (Most expensive GnRH agonist)	[redacted]	[redacted]	[redacted]	[redacted]	9,791

Table 15. Pairwise cost effectiveness results – locally advanced subgroup

Subgroup	Treatment	Absolute cost (£)	Absolute QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
Locally-Advanced (LA) On Treatment	Relugolix	[redacted]	[redacted]			
	Blended GnRH agonist Comparator	[redacted]	[redacted]	[redacted]	[redacted]	10,848
	Triptorelin (Cheapest)	[redacted]	[redacted]	[redacted]	[redacted]	11,420
	Goserelin (Most expensive GnRH agonist)	[redacted]	[redacted]	[redacted]	[redacted]	10,260

Table 16. Pairwise cost effectiveness results – biochemically recurrent subgroup

Subgroup	Treatment	Absolute cost (£)	Absolute QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
Biochemically-Recurrent (BR) On Treatment	Relugolix	[redacted]	[redacted]			
	Blended GnRH agonist Comparator	[redacted]	[redacted]	[redacted]	[redacted]	10,476
	Triptorelin (Cheapest)	[redacted]	[redacted]	[redacted]	[redacted]	11,317
	Goserelin (Most expensive GnRH agonist)	[redacted]	[redacted]	[redacted]	[redacted]	10,157

Table 17. Pairwise cost effectiveness results – mHSPC not castrated subgroup

Subgroup	Treatment	Absolute cost (£)	Absolute QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
mHSPC Not Castrated	Relugolix	[redacted]	[redacted]			
	Blended GnRH agonist Comparator	[redacted]	[redacted]	[redacted]	[redacted]	9,059
	Triptorelin (Cheapest)	[redacted]	[redacted]	[redacted]	[redacted]	10,652
	Goserelin (Most expensive GnRH agonist)	[redacted]	[redacted]	[redacted]	[redacted]	7,416
	Degarelix	[redacted]	[redacted]	[redacted]	[redacted]	60,083*

* SW quadrant of CE plane

Modelled comparators

B3. Incremental cost-effectiveness. The CS only reports base case results for relugolix versus the pooled GnRH agonist comparator, although the model also includes incremental results for relugolix compared with the individual GnRH agonist drugs, as well degarelix in the spinal metastases subgroup (see Results!D40-I46). QALY estimates are the same for the three GnRH agonists due to assumptions in the base case model, but their costs do vary. Please report fully incremental results including the separate GnRH agonists alongside the base case pooled-comparator results.

Due to structural limitations of the model, only three GnRH agonists may be presented at once. As such, the model has been updated to show results for the least expensive GnRH agonist (triptorelin), most expensive (goserelin), and a blended mix of all three GnRH agonists (triptorelin/goserelin/leuprolide).

An overview of the incremental cost-effectiveness results for the wider population (with and without spinal metastases) can be found in the tables (Table 18 & Table 19) below:

Table 18. Fully incremental analysis - broader population

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Triptorelin (cheapest GnRH agonist)	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Blended GnRH agonists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Goserelin (most expensive GnRH agonist)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,224.42	£11,224.42

Table 19. Fully incremental analysis - spinal metastases subgroup

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Triptorelin (cheapest GnRH agonist)	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Blended GnRH agonists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Goserelin (most expensive GnRH agonist)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,652.29	£10,652.29
Degarelix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,952.57	£60,082.51

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit.

Clinical parameters

B4. Testosterone suppression percentage. There is a discrepancy between the percentage of patients with sustained testosterone suppression to castrate levels with relugolix in the HERO trial, as reported in the Shore et al. 2020 paper and CS Table 13 (96.7%), and the value used in the economic model (96.792%). Please explain this difference and correct if appropriate.

This has been identified as an error in the model. The updated version of the model includes the value 96.7%, as reported in the Shore et al. 2020 paper. Although probability of achieving castration is implemented in the model, because there is no impact on PSA progression it has no impact on the incremental cost effectiveness ratio (ICER).

B5. PRIORITY QUESTION: Duration of ADT treatment. Please report on the data and methods used in the Myovant analysis of Symphony claims database mentioned in Appendix O.1.10 and include this source in the References. In addition, please verify the section number mentioned in this section ("Section 5.4 comparators") as it does not exist in the revised company submission.

The data on file is attached with the responses. A graph presenting the data on treatment persistency in the nmHSPC group is presented below (Figure 4).

Figure 4. Treatment persistency in the nmHSPC group

Source: Analysis of 5 Year Symphony Health claims data of prostate cancer patient, looking for months on therapy before or after definitive therapy
RP = Radical Prostatectomy

For ease, Table 20 below presents the numerical values of the treatment persistency for those in the HSPC health states (LA and BR) found in the chart above. The patients on therapy at the beginning of interval are an average of the two different treatment groups who receive definitive therapy (before or after and either receiving radiation or radical prostatectomy) while on GnRH agonist treatment.

Table 20. Patients on therapy at the beginning of interval (by definitive treatment)

Time Interval	Radiation	Radical Prostatectomy	Average treatment persistency
1-3	[redacted]	[redacted]	[redacted]
4-6	[redacted]	[redacted]	[redacted]
7-9	[redacted]	[redacted]	[redacted]
10-12	[redacted]	[redacted]	[redacted]
13-15	[redacted]	[redacted]	[redacted]
16-18	[redacted]	[redacted]	[redacted]
19-21	[redacted]	[redacted]	[redacted]
22-36	[redacted]	[redacted]	[redacted]
37	[redacted]	[redacted]	[redacted]

Section reference clarification: Section 5.4 comparators, rectify to Section B.1.3.3. (Androgen deprivation therapy)

B6. Duration of darolutamide treatment. Please verify the mean duration of treatment for darolutamide in Table 134 (CS Appendix O.1.10). In Fizazi et al. 2019, the median PFS for darolutamide was 36.8 months. The duration used in the company submission refers to the placebo group.

The 14.8 months value used in the model refers to the median duration of treatment in the darolutamide group from the Fizazi et al (2019) publication, not the median PFS.

Taken from Fizazi et al (2019): "*At that time, the median duration of the treatment period was 14.8 months in the darolutamide group and 11.0 months in the placebo group.*".

Utility parameters

B7. Analysis of HERO EQ-5D utility data. Covariates related to castration levels of testosterone suppression were not included in the final GEE regression equation used to calculate health state utilities for the model (CS Appendix P Tables 140 and 141). This was based on the conclusion that results for this covariate were counterintuitive, although the coefficient was statistically significant (Model 3 in CS Appendix P Table 139). Please repeat the regression in Table 140 with castration as an additional covariate, and report whether and how the inclusion of the castration covariate would change the estimated health state utility values (CS Appendix P Table 141).

In the model we have assumed that prior to PSA is equivalent to prior to castration as the indicated population for treatment with relugolix are still hormone sensitive. Prior to receiving any ADT treatment to castrate testosterone, the PSA levels will remain high, as this is one of the key elements of diagnosis. After receiving ADT the testosterone levels are castrated and the PSA levels are lowered. Post castration is also assumed to be equivalent to Post PSA progression, as the testosterone and PSA levels rise despite being on treatment. Considering the above, castration has not been included as an additional covariate in the final GEE regression equation to avoid confounding variables.

B8. PRIORITY QUESTION: General population utility norms. Please update the general population utility norms used for age-adjustment in the model. The economic model uses an old reference (Kind et al. 1999) (CS B.3.4.5 and Table 50), which only reports utilities for two age groups (65-74 and ≥75 years) relevant for the modelled cohort (age 71 at baseline). More recent estimates are available, including the equation reported by Ara and Brazier (Value in Health 2010), and McNamara et al. (Value in Health 2023).

The general population utility norm values used in the model have been updated accordingly using the equation reported from Ara and Brazier. The coefficients of the regression have been updated in “Utilities_General” and the calculations have been incorporated into “Utilcalc”.

B9. PRIORITY QUESTION: Baseline utility. CS Appendix P Table 137 reports the mean utility at baseline for participants in the HERO trial as [redacted], which is used for the nmHSPC on-treatment health state in the economic model (CS Appendix P Table 142). [redacted]

Please adjust the health state utilities in the model to be consistent with general population norms for men of the same age.

The updated model includes changes to baseline utility values. The updated values have been adjusted to align with those from the general population. An adjustment factor (1.09952) was used to adjust all health state utilities accordingly. The calculation for the adjustment factor is as follows:

Highest health state utility = [redacted] (nmHSPC on treatment)

Utility at age 71 according to general population norms = 0.7863403

[redacted]The above adjustment factor was applied to all the health state utilities from the trial data.

These updates in the model are utilised in the model base case via the selection of the “Model-Based” approach on the “Utilities_General” worksheet.

B10. Disutility for injection site reactions: There is a discrepancy between the disutility value of -0.011 reported in the cited source in CS Table 51 (Boye et al. 2011) and the value of zero used in the updated economic model (Utilities_AE!F16). Please explain this difference and if appropriate update the model.

This was an error. Thank you for highlighting this. The AE disutility for injection site reaction has been updated in the latest version of the model.

Resource use and costs

B11. PRIORITY QUESTION: Please provide ‘Appendix Q: Cost and healthcare resource use identification, measurement and valuation’, which is cited as the location of details regarding resource use and costing in section B.3.5 of the updated CS (dated 25/01/24) but was not sent to the EAG. We note that there is another

appendix with the same name as above (Appendix I). Please clarify the correct names of these appendices.

Appendix Q was uploaded as part of the updated submission on 24th January and should provide the required tables. Although named the same, Appendix I refers to the SLR search process for health care costs, but does not contain the required detail when reviewing section B.3.5 of the CS.

Appendix Q should have been available to the EAG from the time of submission, but in case of issues, we also attach it to this clarification response (with an updated title), along with the updated model. The updated Appendix Q is now titled, Dosages and Costs used in the Economic Model. Any prior cross reference to this section withing the main body of Document B, will refer to costs and medicine doses used in the model.

B12. PRIORITY QUESTION: Costs for MACE events. Please provide more detail on the following acute cost calculations: "Fatal MI", "Fatal stroke" and "Other fatal CV" (CS B.3.5.3.1). We could not match these acute costs in national NHS cost data. The provided currency and service codes returned national average unit costs between £73.87 and £811.64, and the weighted average is under the acute cost informed in CS original Appendix Table 145 (£1005.00).

Thank you for highlighting. The original approach took costs from NHS reference costs 2019/20. The service codes are no longer available in the 2021/22 NHS reference costs. As a result, a weighted average of 'Emergency Medicine, Patient Dead on Arrival', service codes 1-3 were used to provide a weighted average cost which equates to £879.24. This has subsequently been updated in the model.

B13. The model uses BNF list prices for docetaxel and cabazitaxel rather than the lower eMIT prices quoted in Appendix K Table 116. However, it was stated in the original CS (B.3.5.1.4) that eMIT prices would be used for generic medicines delivered in hospital, and Table 95 in the original submission cited eMIT as the unit cost source for these two drugs. Please explain this discrepancy.

Thank you for highlighting this. The eMIT price for docetaxel (160mg) is £16.04 and cabazitaxel (£172.09) (25mg/m^2 (1.97m^2 in model). These prices have been updated in the CEM accordingly.

B14. Please verify the daily dose for radium-223 in Table 116. We understand that the correct dose for this technology is 55kBq/kg body weight (see TA412), equivalent to 1.49mci, not 1.35 mci.

Thank you for highlighting this. It is agreed that the dosing referenced in the TA report (TA412) of 55kBq/kg is equivalent to 1.49mci. This has been identified as a typo in the submission. It is agreed that the value in Appendix Q should read 1.49.

B15. Please provide the IQVIA data source concerning the "dispensing data for agonist and antagonist injections dispensed in primary care and hospital" (CS B.3.5.1.5). We were unable to calculate the proportion between services costs for intramuscular administration of leuprolide and other GnRH agonists.

The required data has been uploaded alongside this document, as data on file. This is a data snapshot from June 2023.

B16. Please provide more detail on the intravenous administration costs in CS B.3.5.1.5. The HRG code SB12Z (deliver simple parental chemotherapy at first attendance) returned a national NHS cost of £172.00, lower than the value in the company submission (£362.00).

Thank you for highlighting this. The values in NHS reference costs (2021/22) have been reviewed. A weighted average of the three service codes (DCRDN, OP, Oth) results in a cost of £286.71. This has been updated in the CEM accordingly.

B17. Please verify if there is a typo in section CS B.3.5.2 and original CS Appendix Tables 146 and 147. The company states that 50% of patients will need a "Radiographic or MRI scan" service during the follow-up period. However, both reference sources (TA580 and TA712) assume that 5% will need a radiographic or MRI scan during follow-up.

Thank you for highlighting this. This value is indeed 5% and refers to the follow up costs. The value has been rectified by updating the value to 5% in the CEM. This has been updated in the retitled, Appendix Q; Dosages and Costs used in the Economic Model.

Cost-effectiveness results

B18. PRIORITY QUESTION: The EAG are unable to match the scenario analysis results in CS Table 58 to the results in the economic model. Please identify the correct scenario results and provide an updated economic model if necessary.

An updated economic model has been provided as the base case results have changed.

The new results for the scenario analyses are presented below.

Table 21. Updated scenario analysis results

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs	Incremental QALYs	ICER vs. relugolix
Base-case			[redacted]	[redacted]	£10,518
Carry over period of MACE	6.8	Reducing the carry over risk of MACE to:			
		0 months	[redacted]	[redacted]	£10,951
		12 months	[redacted]	[redacted]	£10,489
Adverse event disutility	Included	Excluded	[redacted]	[redacted]	£10,518
ADT treatment continuation after castrate resistance	yes	Patients no longer receive ADT therapy after becoming castrate resistant (non-metastatic or metastatic PC)	[redacted]	[redacted]	£10,336
No Impact of MACE	RR of MACE	No MACE impact	[redacted]	[redacted]	Dominated

Additional scenario analyses have also been presented. These include:

- Use of Prior MACE population which reflect UK based data.

A scenario analysis was conducted to observe the impact of changing the Prior MACE populations to reflect more UK relevant Data. A study by Cardwell et al (2021) investigates the risk of cardiovascular disease (CVD) using the Scottish Cancer Registry by type of ADT, in a real-world setting (PDF uploaded on NICE Docs with

this response). Data form the article was utilised to determine the initial proportion of individuals who have prior MACE.

The base case uses a study by Albertson et al (2014) without the adjustment factor which was initially incorporated.

The proportion of individuals with Prior MACE in the Cardwell et al (2021) study were calculated. Table 1 in the article presents data for those taking ADT who have had prior CVD related comorbidities. Those in the study with any cardiovascular comorbidities (3,818 individuals) were divided against the total number of individuals on ADT treatment (11,940 individuals) to determine the proportion of individuals with CVD prior to starting treatment for prostate cancer. This equated to 31.98%. This was used to replace the initial proportion of individuals in the Prior MACE population of the model. The results are presented below (Table 22).

Incremental costs, Incremental QALYs and resultant ICER

Table 22. Additional scenario analysis

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs	Incremental QALYs	ICER vs. relugolix
Base-case			[redacted]	[redacted]	£10,518
Prior MACE population	30.4% (Albertsen et al (2014))	Using UK based data to adjust the CEM Prior MACE population			
		31.98% (Cardwell et al (2021))	[redacted]	[redacted]	£10,587

B19. PRIORITY QUESTION: The tornado diagram provided in CS Figure 24 does not match the diagram in the economic model (see Figure 8 and Figure 9 below), and the colours in the legend for low and high parameters do not correspond to

many of the bars. Please provide the correct tornado diagram, updating the model if necessary.

The CEM has been updated with several parameters described above. An updated copy of the CEM has been provided which contains an updated tornado diagram. Figure 5. Updated base case tornado diagram is also presented below for completeness.

Figure 5. Updated base case tornado diagram

B20. The probabilistic sensitivity analysis was run for 500 iterations. The EAG is unable to recreate the same scatterplot in the economic model as the one provided in CS Figure 22. Please provide a justification for only running the PSA for 500 iterations, and an updated scatterplot.

The CEM has been updated with several parameters described above. A copy of the CEM has been provided which contains the updated PSA scatterplot. The updated PSA is provided below for completeness.

Figure 6. Updated PSA scatter plot

From the rolling average ICER for the existing 500 iterations. It shows that there is very small variation in the ICER after the initial 300 iterations. This is why we limited the iterations to 500. The results are presented in the PSA_Figure sheet in the updated CEM. The figure is provided below for completeness.

Figure 7. Rolling average ICER, by PSA iteration

Section C: Textual clarification and additional points

Headings and reference list for CS Document B (and appendices)

C1. The Table of Contents in Document B is limited to level 1 section headings only (B1 – B4); these are lengthy sections with many significant sub-headings which are

not visible currently. Please can all sub-headings be included in the ToC and also include appendices with their full titles.

Accord apologise for the issue here, and have uploaded a list of the contents in Document B to NICE Docs (Contents list .Docx). In creating this, the page numbers have shifted, so if the EAG would like to see an updated version of Document B with this included, please let us know.

C2. PRIORITY QUESTION. Could the company please provide a complete reference list for all refences cited in Document B and all of the appendices. Currently the reference list for the updated version of the CS Document B (v1.0 240124 IM [CON)] only lists references 1 to 57. It is a requirement that a complete reference list is included when the original company submission is received by the EAG.

Apologies for the error with the reference list, which was the result of an EndNote issue on our end. We have attached a full bibliography for the updated submission that was provided on 24th January (Reference list.docx). This contains 248 citations. This differs from the original submission (259) due to some duplicate entries that were identified during our update (as outlined in response to C3).

C3. PRIORITY QUESTION. Please supply full texts for all references cited in the submission. The previously supplied folder 'ID6187 Relugolix Accord PDFs v1.0 170124 IM [CON]' contains 170 full texts yet there are 259 publications in the reference list of the original submission document B. It is a requirement that all available full texts are supplied when the original company submission is received by the EAG.

As mentioned in response to C2, a number of duplicate EndNote citations were identified whilst preparing the updated submission (submitted 25th January). The most up to date dossier has a total of 248 citations. There are 9 duplicate references in our EndNote citation list that we have been unable to remove (85. Sari Motlagh 2022; 110. Jones 2022; 114. NICE 2022; 141. Schroder 2010; 142. Tombal 2010; 143. Crawford 2018; 144. Crawford 2011; 184. Huben 1988; 233. NICE 2016), meaning the total citations should equal 239. 6 citations are data on file (which have been requested elsewhere in the clarification response), meaning there should be 233 publicly available references. 49 of these citations are webpages which have not

been provided as PDFs, and 1 is an abstract that we are unable to find a digital copy of (157. Seely 1987).

We have uploaded an updated folder including 196 PDFs (not including data on file) to NICE Docs. 3 additional data on file references for the HERO trial have been included, and as requested in questions A5, A6, B1 and B5, further data on file documents has also been provided. This accounts for all remaining references in document B, plus a number of references that are in the BIM document but not in the full submission. Please let us know if you identify any further missing references.

C4. Please supply a .RIS file containing all bibliographic references to studies cited in the company submission and appendices.

A RIS file containing all references cited was attached to the original submission. However, for completeness, Accord have uploaded this to NICE Docs in response to this question. Any discrepancy in number of references is due to issues with duplicate entries, as well as inclusion of references cited in the budget impact analysis form.

Appendix

Figure 8 Tornado diagram provided in CS Figure 24

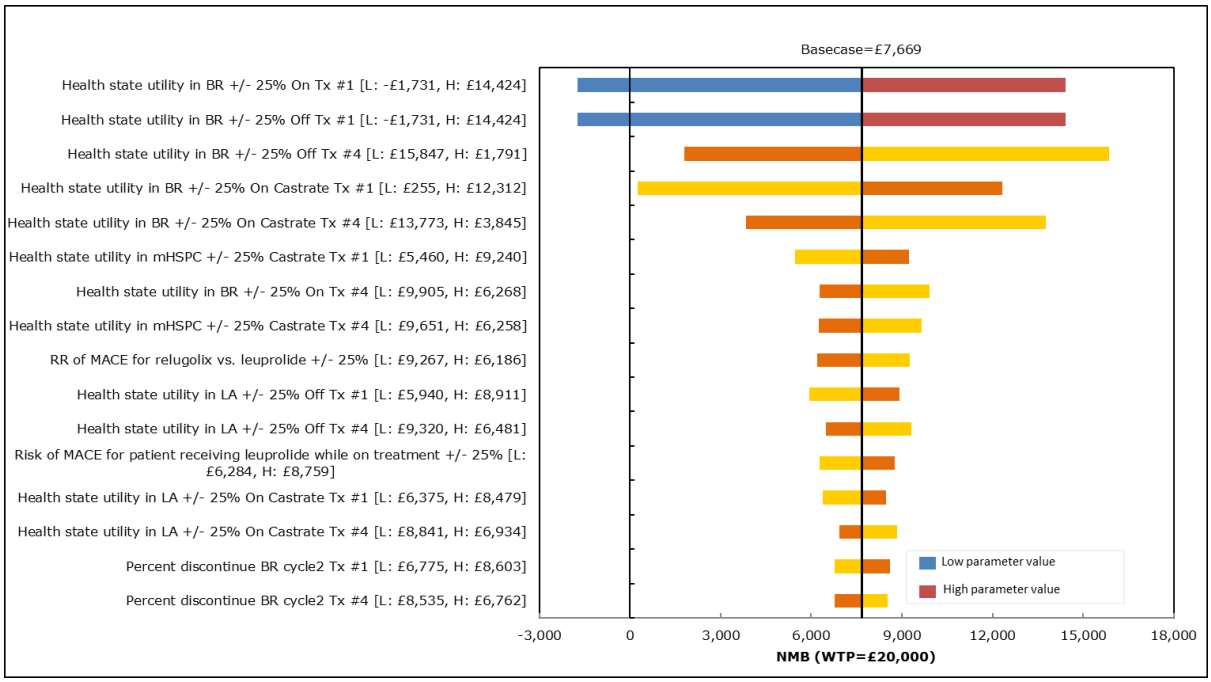


Figure 9 Tornado diagram provided in the company economic model

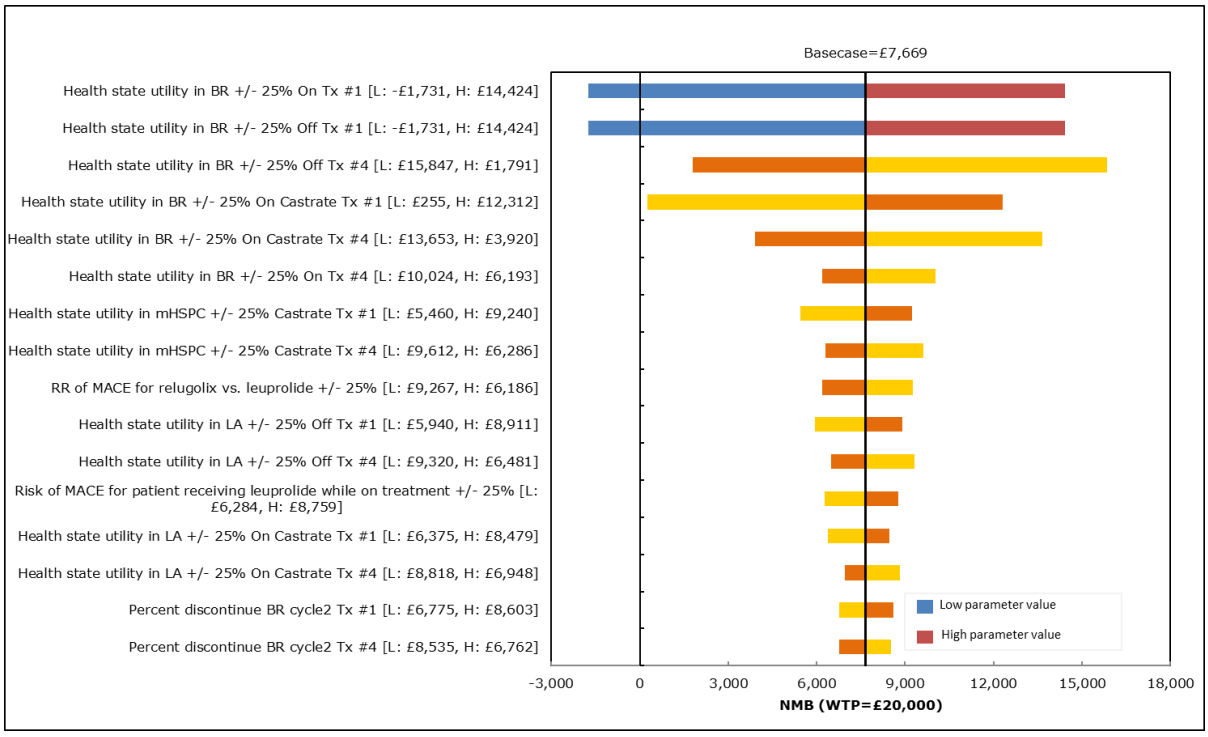


Figure 10 Scatterplot of PSA simulations provided in CS Figure 22

Figure 11 Scatterplot of PSA simulations from company economic model

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Prostate Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer UK is a voluntary organisation based in London. It is a registered charity in England and Wales (1005541) and in Scotland (SC039332). Registered company number 02653887.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Accord Healthcare Limited – N/A Myovant Sciences – N/A AstraZeneca – 2022 £10,350.– Prostate cancer UK Improvement Programmes Ferring Pharmaceuticals – N/A Ipsen (triptorelin) - N/A Neon Healthcare – N/A Takeda – N/A Typharm – N/A
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Via our clinical nurse specialists and talking directly with a patient who has experience of having relugolix.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Although prostate cancer affects each patient differently we know that a diagnosis of metastatic prostate cancer initially causes fear, distress and anxiety for the patients and their families. Many will live for some years with advanced prostate cancer but the incurable nature of advanced disease can, for some, be very difficult to manage psychologically. Some patients will initially be asymptomatic whilst others may experience or develop symptoms, often bone pain. Whilst the prostate cancer is responding to first line hormone therapy, many patients and their families can establish a fulfilling lifestyle as this treatment can result in prolonged control. However, anxiety is often reported during this stage as a patient will be anxious when their next (often 3 monthly) PSA blood test is due. This is because an elevated PSA level can indicate the response to the hormone therapy they are receiving is decreasing. Each time a treatment is no longer controlling their disease, fear and uncertainty about the future can return with the subsequent impact on quality of life. As advanced prostate cancer progresses, men may experience different symptoms (depending on where their cancer is) from their prostate cancer including those below: Pain may develop and for some men this can be significant. Clearly this is distressing for both men and their families as well as having an impact on quality of life. Men with advanced prostate cancer who have bone metastasis, including in the spine, may develop spinal cord compression. These men require urgent treatment to prevent permanent nerve damage and potential paralysis. This can be a debilitating and life-changing problem. Bone metastasis can also result in spontaneous fractures, without trauma and increased risk of fracture associated with trauma. For men whose prostate cancer affects their bone marrow, they may become anaemic (so be more tired or become breathless) requiring blood transfusion, thrombocytopenic (be more prone to bruising and bleeding) and low white blood cell counts (making them more susceptible to infection). Visceral metastases most commonly involve the liver and the lungs, causing considerable and intractable morbidity; Brain metastases commonly result in significant and distressing neurological deficits. Weight loss and reduced appetite can often be a particular concern for carers. If prostate cancer advances in the region around the prostate, men may experience urinary tract problems and renal problems. Patients might also have other comorbidities that affects them.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Currently patients who have become metastatic but are still responding to hormone therapy have a few treatment options available to them. These include leuprorelin acetate (Prostap) or goserelin (Zoladex) with docetaxel or Novel Hormone Agents (Abiraterone and Enzalutamide). Those patients who have metastatic prostate cancer and are responding to hormone therapy but who are unable to have docetaxel can have Apalutamide plus ADT. These treatments provide a number of options to those who are hormone sensitive metastatic where curative treatment is not a possibility. Leuprorelin acetate and goserelin are administered through injection, which can in some cases cause poor side effects for patients such as infection and sepsis at the injection site. Due to this, there is a strong need for more varied treatments to be available to bring a more tailored approach for these patients.
8. Is there an unmet need for patients with this condition?	We believe that currently some patients are missing out on the benefit of taking this treatment. Relugolix is an oral treatment and so has benefits of not having to travel to a GP or hospital setting for injection as is the case with the comparators. Some patients who we have spoken to are unable to have injections due to anxiety or physical reactions to the administration, these patients would benefit greatly from an oral treatment. Relugolix also has shown superior suppression of testosterone when compared to leuprolide. This potential for more superior testosterone suppression in relation to comparators is a benefit a lot of patients would want from their treatment.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	As previously stated one of the key advantages of the technology is that relugolix is administered in tablet form rather than injection, compared to leuprolide use in the HERO trial which requires injections every 3 months and compared to leuprorelin acetate which requires injections as in the case of the patient to whom we spoke. This may increase uptake in patients, as they are freed up from requirements to travel or take time off work for administration. It is particularly of benefit to those unwell with other co-morbidities, disabilities, those who are unable to travel or live far away from a clinic. Also, there would be a strong advantage of taking reluglox for those who have a fear of needles or experience poor side effects of injections such as swelling and infection. Treatment adherence with oral relugolix was more than 99% in the HERO trial. Moreover, less clinical time is required for relugolix as it isn't required to be administered in a clinical setting such as the GP or hospital by a health professional. Relugolix is a good option for those who don't react well to leuprorelin acetate or injections. The patient we interviewed on relugolix had a raised temperature and swelling following an injection of leuprorelin acetate, following a subsequent injection they were referred to hospital as an abscess had formed and needed to be drained. The recovery time from this operation was 2 months, alongside the patient's other comorbidities such as blood cancer, this had a very negative impact on his health and how he was feeling about his health. He reported that if he was due to have another injection, he would feel very apprehensive and anxious waiting for it and worry about having side effects again. This patient also reported fewer hot flushes that were less pronounced compared to leuprorelin acetate. The patient reported that their partner also felt relieved once they started relugolix, due to the reduced side effects compared to injections. According to the HERO trial, there was a 54% lower risk of major adverse cardiovascular events in patients taking relugolix than those taking leuprolide. Also, relugolix achieved a superior suppression of testosterone levels to that of leuprolide. In the HERO trial, of men who received relugolix, 96.7% (95% confidence interval [CI], 94.9 to 97.9) maintained castration through 48 weeks, as compared with 88.8% (95% CI, 84.6 to 91.8) of men receiving leuprolide. The percentage of patients with castrate levels of testosterone on day 4 was 56.0% with relugolix and 0% with leuprolide.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As an oral application, this can be taken at home daily; there may be a potential issue with regards to compliance to this medication regimen compared to less regular injection, in a real world setting. However, it's important to note that in trial context, there was no difference in treatment adherence observed when using oral therapy vs injectable leuprolide.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	More than 90% of the patients involved in the HERO trial had at least one cardiovascular risk factor, which included lifestyle risk factors such as tobacco use and obesity, cardiovascular risk factors such as diabetes and hypertension and a history of a major adverse cardiovascular event. Therefore, patient populations with these risk factors and comorbidities might benefit from taking relugolix due to the decrease in the rate of major adverse cardiovascular events compared to other treatments. Those who react poorly to injections will particularly benefit from this technology. Several patients have reported having poor side effects, including swelling, abscesses and skin reactions from injection treatments such as goserelin and leuprorelin acetate. One patient reported side effects so extreme from goserelin that they have considered stopping treatment entirely. The oral administration of this drug will especially benefit the physical and mental wellbeing of these patients.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We consider the draft remit to be sufficient with regards to the equality aims. This drug may be beneficial for those who have co-morbidities, would have long distances to travel for injection (as with the administration of leuprolide), or disability, compared to other options. However, Black men are not represented in the trial as patient subgroups are only broken down by North and South America, Europe and Asia Pacific rather than by ethnicity. Baseline risk for Black men with cardiovascular risk factors and diagnosis of advanced prostate cancer may lead to different outcomes.

Other issues

13. Are there any other issues that you would like the committee to consider?	1. The company should help produce a list of UK P-Glycoprotein (P-GP) inhibitor drugs (taken orally for cardiovascular disease) which interact with relugolix – an issue detailed in European Market Authorisation documents 2. Important to examine any available data on the relative harm of combined/staggered treatment with orchidectomy and relugolix in terms of incidence of bone fracture compared with another available treatment such as Leuprolide?
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• We believe that some patients are missing out on the benefits of taking this treatment. Relugolix is an oral treatment and so has benefits of not having to travel to a GP or hospital setting for injection as is the case with the comparators. Some patients who we have spoken to are unable to have injections due to anxiety or physical reactions to the administration, these patients would benefit greatly from an oral treatment. • Relugolix also has shown superior suppression of testosterone when compared to leuprolide. This potential for more superior testosterone suppression in relation to comparators is a benefit a lot of patients would want from their treatment • According to the HERO trial, there was a 54% lower risk of major adverse cardiovascular events in patients taking relugolix than those taking leuprolide. • As an oral application, this can be taken at home daily; in a real world setting there may be a potential issue with regards to compliance to this medication regimen compared to less regular injection within a clinical setting.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Relugolix for treating hormone-sensitive prostate cancer [noCON]

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	**Stephen Allen**
2. Name of organisation	**TACKLE Prostate Cancer**
3. Job title or position	**Patient Representative and Trustee**
4a. Brief description of the organisation (including who funds it). How many members does it have?	Tackle is a patient centred charitable organisation whose aims are to support men and their families whose lives are affected by prostate cancer. In addition we aim to represent the opinions of patients on any subject which is relevant to the diagnosis and treatment of prostate cancer. We also support local prostate cancer support groups around the UK. We represent nearly 120 support groups in England and Wales and through them have several thousand individual members - men and their families whose lives have been affected by prostate cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	**YES** Tackle Prostate Cancer have provided 2 patient members (Dr Stephen Allen & Mr Andrew Gabriel) to act in an advisory capacity to Accord Pharmaceuticals. Alongside two oncology consultants they helped design materials to be used as part of structured interviews and an on-line questionnaire commissioned by Accord to act as a patient forum to assess patient views on hormone therapy The representatives did not have any direct contact with patients participating in these interviews/surveys. Tackle advertised both studies to our membership. We did not promote the product.

If so, please state the name of the company, amount, and purpose of funding.	Tackle as a Charity received an unrestricted grant of £5k from Accord once all survey activities were completed. Neither individual involved received personal financial reward from the company.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
5. How did you gather information about the experiences of patients and carers to include in your submission?	Gathering regular input from our members is a priority, and we achieve this through various channels such as at local and national meetings online as well as in person. Additionally, we engage in direct communication with individuals and address questions and concerns raised by patients through our dedicated patient helpline. Our medical advisory board is in place to offer guidance whenever necessary. While the treatment currently under evaluation is not yet accessible through the NHS, conventional hormone/ADT therapy administered via depot injection is widely utilised in prostate cancer treatment. The challenges associated with ADT are frequently discussed among patients in support groups and on helplines, focusing on the side effects and often on the inconvenience of regular injections. I am confident in my ability to comprehend the needs of patients undergoing hormone therapy, making it fitting for me to advocate on their behalf.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Individuals with metastatic prostate cancer are aware of the gravity of their situation. They will have been informed that Androgen Deprivation Therapy (ADT / hormone therapy) serves as an effective method for managing prostate cancer growth by inhibiting testosterone production. It is understood that while ADT does not constitute a definitive 'cure,' it can exert prolonged control over the cancer. The unavoidable consequence of significantly lowered or zero testosterone levels includes side effects such as diminished libido, reduced sexual function, fatigue, weight gain, hot flushes, and breast tenderness. These side effects are commonly experienced to varying degrees by the majority of patients undergoing this treatment. Because this treatment can undeniably prove effective, patients often find themselves compelled to endure the associated side effects, often with limited alternatives. Presently, all ADT formulations involve injections, requiring careful planning and the involvement of healthcare professionals / nurses, typically in General Practice settings. However, for some patients, this injection-based treatment can be an unpleasant and painful experience, and arranging regular injections may pose significant challenges at times. Access to general practice services is increasingly less easy in certain regions of the country. Many patients may already be on regular oral medication for other reasons, making the prospect of receiving hormone therapy through a simple daily oral dose highly appealing. Quality of life is a crucial consideration for patients at any stage of their disease. Having an easily accessible route for their treatments is highly desirable. The journey of prostate cancer treatment involves substantial emotional fluctuations for patients, family members, and caregivers. This new treatment holds the potential to simplify the method of treatment, providing a more accessible and manageable approach for all involved parties.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The majority of existing ADT treatments are GnRH agonists, inhibiting testosterone production by the testicles. However, they trigger an initial surge in testosterone, necessitating a subsequent period of temporary androgen receptor blockade, typically achieved orally with Bicalutamide. This step aims to prevent the initial stimulation of prostate cancer growth before suppression occurs. Degarelix stands out as the sole current drug that avoids the initial testosterone surge. It boasts a faster onset of action compared to other preparations and is generally reserved for situations demanding a rapid reduction in testosterone levels, such as instances where spinal cord compression from a secondary tumour is likely. However it is still requires administration by injection. The selection of ADT drug to be prescribed can sometimes appear somewhat arbitrary, influenced by factors such as the clinician's preference, product availability, and even the cost of individual products. It is generally assumed that all comparator preparations are equally effective in reducing testosterone levels and are thus interchangeable. Some injectable products can be more painful that others when administered to patents. The HERO trial showed Relugolix to be as effective as Leuprolide and in some regards superior. All ADT drugs carry a significant side effect profile, yet most patients tend to accept these side effects given the effectiveness of the treatment. The HERO study shows the side effect profile of Relugolix to be very similar to standard ADT, and better in some regards - particularly the incidence of major cardiovascular events. Given the average age of the patients likely to need ADT, this may well be important.

8. Is there an unmet need for patients with this condition?	While many patients may require long-term ADT therapy, some may only need it for shorter periods, such as before and after surgery or in conjunction with radiotherapy. For these patients, a predictable and swift return of testosterone levels to normal after successful additional therapy can be crucial in assessing overall quality of life. Relugolix offers the advantage of rapidly reducing testosterone levels upon administration and facilitating a swift return to normal levels when treatment is halted. This characteristic time course makes it particularly valuable for patients requiring such dynamics in their treatment. Equally important is that oral administration is a major benefit compared to current injectable treatments. Whilst there will be patients who will prefer to have periodic injections, there will be those who would prefer a simple once daily tablet. Relugolix now offers that choice of treatment route. This is a major innovation in the use of ADT. There is certainly an unmet need.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The swift reduction of testosterone levels and the quick return to normal levels after stopping treatment are important factors, especially for patients undergoing surgery or radiotherapy as primary therapy and may not need ADT in the long term. The option of oral administration over injectable treatments can be a significant advantage for some patients, as it offers a more convenient and potentially preferable mode of treatment and provides flexibility in managing treatment dynamics. The choice between periodic injections and a once-daily tablet allows for a more personalised approach, addressing individual patient preferences. In summary, Relugolix appears to be a promising option in ADT, offering a faster and more flexible treatment approach that could positively impact the overall experience and quality of life for patients undergoing androgen deprivation therapy.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The HERO study indicates a comparable set of side effects between Relugolix and leuprolide and, in certain aspects, the side effect profile of Relugolix may even be superior. There appears to be minimal disadvantage associated with the use of Relugolix in comparison with standard ADT.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Some individuals may find it unacceptable to add another tablet to their existing medication regimen. Additionally, patients with compromised cognitive function, who already face challenges in remembering to take oral medication, might prefer periodic injectable therapy. Currently, the crucial element is the lack of choice for patients in this regard.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	NONE

Other issues

13. Are there any other issues that you would like the committee to consider?	**NO**
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Hormone therapy (ADT) is a fundamental component in treating metastatic prostate cancer, demonstrating high effectiveness in managing cancer progression. • The side effects of ADT are virtually unavoidable for the majority of men due to the inherent cessation of testosterone production. • All existing forms of ADT seem to be equally proficient in controlling cancer growth. Notably, Relugolix has proven to be on par with or even superior to Leuprolide, particularly in terms of the rapid onset and recovery of testosterone levels. • Relugolix introduces a novel approach to effective ADT through a convenient daily tablet, distinguishing itself as the sole oral treatment of its kind in this regard.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with hormone-sensitive prostate cancer or caring for a patient with hormone-sensitive prostate cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with hormone-sensitive prostate cancer

Table 1 About you, hormone-sensitive prostate cancer, current treatments and equality

1. Your name	Stephen Allen
2. Are you (please tick all that apply)	☐ A patient with hormone-sensitive prostate cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with hormone-sensitive prostate cancer? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Tackle Prostate Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with hormone-sensitive prostate cancer? **If you are a carer (for someone with hormone-sensitive prostate cancer) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for hormone-sensitive prostate cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for hormone-sensitive prostate cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of Relugolix over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	

9c. Does Relugolix help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of Relugolix over current treatments on the NHS please describe these. For example, are there any risks with Relugolix? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from Relugolix or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering hormone-sensitive prostate cancer and Relugolix? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Single Technology Appraisal

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Patient expert statement

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Patient expert statement

Part 1: Living with this condition or caring for a patient with hormone-sensitive prostate cancer

Table 1 About you, hormone-sensitive prostate cancer, current treatments and equality

1. Your name	Peter Rose
2. Are you (please tick all that apply)	☒ A patient with hormone-sensitive prostate cancer? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with hormone-sensitive prostate cancer? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Prostate Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with hormone-sensitive prostate cancer? **If you are a carer (for someone with hormone-sensitive prostate cancer) please share your experience of caring for them**	**Medical background** I am aged 69 and retired. My experience of and treatment for prostate cancer needs to be considered in the context of my earlier diagnosis for a blood cancer in September 2019 – Myelodysplastic Syndrome (MDS). As a result of this I am somewhat anaemic and in particular severely neutropenic, so tending to be fatigued and at risk of infections. One consequence of this has been that I have generally avoided situations where there may be a lot of people close together, such as cinemas and theatres, and I have dropped out of a couple of music groups that I used to play in. I have been less confident about committing to things such as holiday trips, as my health can be a bit up and down. So the prostate cancer, its treatment, and my response to it needs to be seen against that background, and it means that it is hard for me to know what to put down to MDS and what to put down to prostate cancer and its treatment. In January 2023 I was diagnosed with low volume metastatic prostate cancer. I was initially prescribed Enzalutamide and injections of LHRH protagonist (leuprorelin acetate – Prostap). This came with the typical side-effects of increased fatigue and hot flushes. After the second Prostap injection in Feb 2023 (buttock) I had a raised temperature and the injection site was sore and swollen for a number of days. After the third Prostap injection in May 2023 (abdomen) the site became swollen, tender and infected. I was admitted to hospital for an abscess to be drained under general anaesthetic; the wound took two months to heal, with the dressing being replaced regularly at the GP surgery. Oncology staff thought that most likely I was

	susceptible to infection because of the MDS and concluded that the Prostap injections were not appropriate. Instead they prescribed Relugolix, which I have taken since August 2023, alongside the Enzalutamide. Hot flushes seem fewer and less intense. Fatigue may be greater, though it is hard to know the cause; for example, my haemoglobin levels have dropped a bit over the last year, but I don't know whether this has affected my fatigue levels and whether this is an effect of the MDS, or the hormone treatment. My PSA has continued to drop and in April 2024 was 0.20. **Impacts** I wasn't aware of any particular symptoms associated with the prostate cancer itself ahead of diagnosis, and I am still not, presumably because the hormone therapy is doing its job (touch wood!). As noted above, it is hard to disentangle the effects of Relugolix plus Enzalutamide from other ongoing health issues, particularly the MDS. I am fine with the daily routine of cooking, housework, light DIY, shopping etc, but I don't feel so confident about, say, a DIY project requiring sustained effort, or a walk longer than say 45–75 minutes (mostly less than this at the moment). I have been joint editor of a local journal, but I have recently stepped down from this, partly because I wasn't sure I could sustain it. I find it harder to get motivated to do things, such as outings beyond the nearest few miles, or something outside the familiar routine, or that adds to stress, though again this has probably been the case since diagnosis with MDS in September 2019. I have asked my partner how my prostate cancer and its treatment have impacted upon her and her quality of life. She says that the main change and impact came with the diagnosis of MDS, and that the prostate cancer has not so far made a big change to that.
7a. What do you think of the current treatments and care available for hormone-sensitive prostate cancer on the NHS?	My experience is of a very expert and caring oncology staff, who have a wide range of effective treatments available. Treatments without the side effects would be even better!

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of current NHS treatments for hormone-sensitive prostate cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	From my own experience, I have to note in particular the risk of infection from LHRH Prostap injections. Other side effects such as fatigue have an impact on the quality of life (see question 6). (I can imagine this could be particularly serious for someone who is still in employment.)
9a. If there are advantages of Relugolix over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Relugolix help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	For me, the main advantage of Relugolix is that it has taken away the risk of infection arising from the Prostap injections. I would have been worried about having further Prostap injections, after the effect of the last one on 11 May 2023, so it has been a relief to me, and my partner, that I have been able to use the Relugolix as an alternative.
10. If there are disadvantages of Relugolix over current treatments on the NHS please describe these. For example, are there any risks with Relugolix? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I'm not aware of particular disadvantages or risks compared to other treatments. Potentially there is the risk of forgetting to take the daily tablet, but in practice with a regular routine I don't find this a problem.
11. Are there any groups of patients who might benefit more from Relugolix or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	Related to my own experience, patients at risk of infections arising from Prostap injections would benefit from Relugolix. Otherwise, I can see that some people might be worried about needles and injections in general, so Relugolix would be an advantage for them. Also, some may

dexterity or cognitive impairments) that affect the suitability of different treatments	have difficulties in getting to a clinic for an injection, whether for mobility issues or due to work and personal commitments.
12. Are there any potential equality issues that should be taken into account when considering hormone-sensitive prostate cancer and Relugolix? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I'm not aware of anything here in relation to Relugolix. More generally, though, I would imagine that this condition and its treatment would have a greater impact on working people and younger people looking to start or raise a family.
13. Are there any other issues that you would like the committee to consider?	No.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- In my experience Relugolix has been an effective alternative to Prostap injections, which have caused me infection needing hospital treatment.
- The infections may have arisen from my background blood cancer, Myelodysplastic Syndrome, which means I am severely neutropenic (and somewhat anaemic).
- Because of my pre-existing MDS it is hard to disentangle the effects of MDS from those of the hormone therapy.
- It is a relief to me that I don't have to risk infection from Prostap injections, and I would be worried about having to start them again.
- Click or tap here to enter text.

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Single Technology Appraisal

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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Part 1: Treating hormone-sensitive prostate cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Jonathan Aning
2. Name of organisation	British Association of Urological Surgeons
3. Job title or position	Consultant Urological Surgeon and Honorary Associate Professor
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hormone-sensitive prostate cancer? ☒ A specialist in the clinical evidence base for hormone-sensitive prostate cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
8. What is the main aim of treatment for hormone-sensitive prostate cancer?	Androgen deprivation therapy (also referred to as hormone therapy in the prostate cancer field) is the cornerstone of treatment for advanced prostate cancer. The main aim of treatment for hormone sensitive metastatic prostate

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	cancer is to improve overall survival. Currently androgen deprivation therapy achieves this by reducing circulating testosterone and maintaining disease control for as long as possible before progression to metastatic castrate resistant prostate cancer.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Clinically significant treatment responses: - Achieving and maintaining castration levels <50 ng per deciliter - Achieving delay / improvement in the progression of metastases - Reduction in skeletal metastases related events - Achieving improvement in cancer survival and overall survival compared to no treatment
10. In your view, is there an unmet need for patients and healthcare professionals in hormone-sensitive prostate cancer?	Currently approved effective methods of androgen deprivation therapy utilising LHRH analogues in the UK are all delivered by injection (subcutaneous / intramuscular) at 1/3/6 monthly intervals. Median overall survival for patients with metastatic hormone sensitive prostate cancer on androgen deprivation alone is around 50 months, regular injections can impact on quality of life for patients. Currently a trained health care professional is required to inject LHRH analogues leading to the patient having to attend a primary care appointment to receive treatment. An alternative to injections and regular primary care attendances is an unmet need. Strategies to address the side-effects of Androgen Deprivation Therapy and Survivorship are also an unmet need in this patient group.
11. How is hormone-sensitive prostate cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	Standard treatment of metastatic hormone sensitive prostate cancer presently is an injected LHRH analogue / orchiectomy in addition to either an androgen-receptor pathway inhibitor and/or docetaxel chemotherapy in patients with a good performance status.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	If an LHRH agonist is prescribed, an oral antiandrogen may also be given at initiation of treatment to prevent flare Intermittent androgen deprivation therapy may be offered to counselled patients with hormone sensitive metastatic prostate cancer. In current practice, radiotherapy is a treatment option for patients with localized prostate cancer. These patients technically also have hormone sensitive prostate cancer. Radiotherapy is currently delivered in combination with androgen deprivation therapy as the relative risk reduction for disease progression and metastatic relapse have been demonstrated to be improved when radiotherapy is given in combination with androgen deprivation therapy. Androgen deprivation therapy prescribed in this scenario is given for a defined time period between 6 months and 3 years. Guidance from NICE, EAU and The Royal College of Radiologists, Clinical Oncology support this practice. The pathway of care for these patients is well defined and there is consensus that fundamentally ADT in the form of an LHRH analogue / orchiectomy form the mainstay of treatment for the patient groups described above. In the majority of UK centres once androgen deprivation therapy has been initiated, my opinion and experience is that most LHRH analogue prescriptions and treatment delivery will take place in primary care under the guidance of advice from secondary care. An LHRH antagonist oral alternative would potentially decrease the healthcare resource usage related to the delivery of the LHRH injection in primary care as patients would not need to attend their surgery for an injection.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently most LHRH analogues are given life long after diagnosis of metastatic prostate cancer and for a defined period when used in combination with radiotherapy. The proposed technology would be used in the same way as in current NHS clinical care.

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Healthcare resource use will differ with the present technology compared to current care because patients would not be required to attend for an LHRH analogue injection. This treatment should be used in the primary and secondary care setting No major investment is needed from the NHS to introduce this technology (other than the cost of the medication) – urologists, oncologists and primary care are already familiar with androgen deprivation therapy. The novel aspect of this technology is the method of delivery – therefore updated information regarding the dose, side effect profile, indications and contraindications as with any medication would need to be disseminated.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I am not aware of any evidence that indicates that the technology will increase length of life more than current care. I am not aware of any evidence to support potential to increase health related quality of life more than current care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology would be more effective for: - Needle phobic patients - Patients group in whom a rapid decrease in testosterone is desirable - Could be considered in patients who are unable to easily access primary care services - Patients who suffer significant side effects from ADT as stopping oral medication may lead to a more rapid return to baseline testosterone level This technology would be less effective for: - Patients with relative / absolute contraindications

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	This technology would be easier to use for compliant patients and easier for the health system potentially to administer than the present injectable LHRH analogues. Current monitoring whilst on treatment would remain unchanged. Patient compliance will be evident through current review practice where PSA and Testosterone levels are measured.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No new rules or additional testing should be needed to guide starting or stopping treatment from a clinical perspective.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	With this technology because it is a novel oral alternative to present standard of care, it may be more easily administered (taken at home) and negate the need for travel to a primary care facility this may not be captured fully in the QALY calculation.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	An oral LHRH analogue represents a 'step change' in the management of prostate cancer as it both provides patient choice (which has not been an option until now) and potentially is easier to administer for the system. The technology addresses the unmet need of providing an alternative to treatments delivered by injection and reducing regular primary care attendances.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile of Relugolix is from the studies that have been published similar to the side effects suffered by patients undergoing injectable treatment. In the phase 3 HERO study there were a higher percentage of patients reporting mild/ moderate diarrhoea but no patient was withdrawn for this reason. The return to a normal range testosterone reported in the HERO phase 3 study ('The percentage of patients with testosterone recovery to at least 280 ng per deciliter (the lower limit of the normal range) at 90 days was 54% in the relugolix group and 3% in the leuprolide group (nominal P=0.002)') is interesting but has not been fully related to patients side-effects after treatment -
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials on the technology represent men with hormone sensitive prostate cancer. Adherence rates detailed in published studies are greater than 90%. In the phase 3 HERO study a heterogenous cohort or patients with prostate cancer were included of which the largest cohort was biochemical recurrence / clinical relapse after primary treatment with curative intent. UK centres contribute patients to the trial (Scunthorpe, Glan Clwd, Royal Devon and Exeter NHS Trust, Nottingham University Hospitals NHS Trust). The primary end point of the phase 3 HERO trial was sustained testosterone suppression to castrate levels through 48 weeks – whilst clinically relevant outcomes described above in response 9 were not end points in this study, because the castration status was achieved consistently there is no reason to believe that similar outcomes to other LHRH analogue outcomes would not be achieved. Similarly in phase 2 work by Dearnaley D et al. Eur Urol 2020. Rate of effective castration only in an external beam radiotherapy population was examined as the primary outcome.

	I am not aware of any adverse effects that have come to light which were not apparent in clinical trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Real world data seems to reflect the trial data tolerability findings. Specifically with regard to UK standard of care practice in the management of hormone sensitive metastatic prostate cancer the following abstracts describe selected real world US experience. Real world experience has been studied in the US: Abstract 74 (Journal of Clinical Oncology 2023 suppl 74) The percentage of Relugolix use in combination with other Prostate Cancer medication was frequently observed and higher in patients on Relugolix. There is little data on tolerability / safety in real world populations when combined with androgen signaling inhibitors: Abstract 85 (Journal of Clinical Oncology 2024 suppl 85) looks at this and concludes a favourable profile with no new safety concerns.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	I am not aware of any equality issues that need to be taken into account. All eligible patients with hormone sensitive prostate cancer needing treatment should in principle be given equal access to available medication if they have no contraindications. The choice of an oral agent would in my opinion likely improve access and choice for patients rather than disadvantage them. I have examined the phase 3 HERO publication and associated supplementary material, I did not find any information regarding the ethnicity of participants detailed so cannot comment on this perspective.

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Relugolix offers a novel oral alternative to the current injectable methods of androgen deprivation therapy

The reported side effect profile seems similar to other LHRH analogues

Although in the phase three HERO study the cohort was heterogenous, and no overall survival data is available; from the perspective of achieving castration Relugolix is evidenced in the short to medium term to be non inferior to other methods of Androgen Deprivation therapy.

For patients who are needle phobic / cannot access primary care services there is clear benefit in having this treatment as an alternate option

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Single Technology Appraisal

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating hormone-sensitive prostate cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr. Amarnath Challapalli
2. Name of organisation	British Uro-oncology Group (BUG)
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hormone-sensitive prostate cancer? ☒ A specialist in the clinical evidence base for hormone-sensitive prostate cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for hormone-sensitive prostate cancer?	In patients with localised prostate cancer – the aim is to cure it. In patients with advanced prostate cancer – the aim is to stop progression, improve overall survival and improve/maintain quality of life.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Localised prostate cancer – PSA response and durability of PSA response; Metastatis Free Survival. Advanced prostate cancer - Optimising quality of life and improving radiological progression free survival, and overall survival.
10. In your view, is there an unmet need for patients and healthcare professionals in hormone-sensitive prostate cancer?	In localised prostate cancer – there is prolonged time to testosterone recovery after stopping adjuvant ADT. Patients with metastatic disease do have co-morbidities and are at Increased risk of cardiovascular side-effects with indefinite ADT. The unmet need is lack of ADT options with favourable cardio-vascular side-effect profile. Relugolix will be an effective option with its favourable cardio-vascular side-effect profile, which will plug the unmet need. The potential recovery of testosterone over a short frame of time after stopping treatment is an important aspect for patients who suffer from intolerable side-effects related to castration.
11. How is hormone-sensitive prostate cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Hormone sensitive prostate is managed as per NICE guidelines – which recommend starting ADT as part of treatment in high risk localised prostate cancer. The NICE guidelines also recommend ADT as mainstay of treatment in patients with metastatic disease. Relugolix will be an additional option for ADT but with a favourable cardio-vascular side-effect profile.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Relugolix will be a new GnRH antagonist option for ADT treatment in localised and metastatic prostate cancer. The use of relugolix will avoid need for personnel for administering injections in primary care. It will also reduce the resources required for managing cardio-

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	vascular effects in the long term. Also, the practice of giving an antiandrogen to cover the first LHRHa injection to prevent flare will not be required saving resources and importantly streamlining patient care pathways. Relugolix can be adminsitered in the primary care setting. There is no need for any investment to introduce the technology. It is already being used to manage severe symptoms of uterine fibroids.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The technology will have a significant positive impact on patients quality of life with faster testosterone revovery times and less cardiovasuclar side-effect profile. This will reduce health care resource utilisation in the long term.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Similar to degarelix, relugolix can be more useful for patients with spinal metastases with impending cord compression or patients at risk of urinary outflow obstruction.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Relugolix will potentially be easier for patients as it will reduce the visits for LHRHa injections as it is an oral medication which can be self administered by the patients.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The favourable cardio-vascular side-effect profile will need to be taken into account in the QALY calculations. As it is an oral medication – there is lesser healthcare resource utilization, which also needs to be factored in.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The faster testosterone revovery times and less cardiovasuclar (CVS) side-effect profile will give substantial benefits.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As per the HERO trial, the lower incidence of CVS sde-effects with Relugolix will have a favourable effect on patients QoL. Patients on Relugolix had a lower burden of hormone related symptoms.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	The patients included in the HERO trial reflect the UK population.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	There are currently no real world data available in the UK. The REAL-ADT combo study shows that ARTA's are commonly used in combination with Relugolix. The OPTYX study is also underway in the USA.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	No

• lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Relugolix is an oral GnRH antagonist which can self administered

The testosterone recovery after stopping Relugolix is quick and reduces hormone related symptoms

Relugolix has a favouravle cardiovascular side-effect profile

Relugolix will reduce visits for LHRHa injections and avoids needs for anti-androgens for preventing flare, thus reducing costs and streamlining patient pathway

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Post factual accuracy check ERRATUM

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Declared competing interests of the authors and advisors

The EAG and the clinical advisor declare no competing interests.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Marcia Takahashi critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Emma Maund critically appraised the clinical effectiveness systematic review and the company's network meta-analysis, and drafted the report; Asyl Hawa critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Scott critically appraised the company's network meta-analysis and drafted the report; Joanne Lord critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Jonathan Shepherd critically appraised the clinical

effectiveness systematic review and critically appraised the company's network meta-analysis, wrote the report, project managed the review and is the project guarantor.

Commercial in confidence (CIC) information in blue

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AIC	Academic in confidence
ARI	Androgen receptor inhibitor
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DSU	Decision Support Unit
EAG	External Assessment Group
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
GnRH	Gonadotrophin-Releasing Hormone
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HSPC	Hormone Sensitive Prostate Cancer
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IM	Intramuscular
IPD	Individual patient-level data
ITC	Indirect treatment comparison
ITT	Intent to treat
MACE	Major Cardiovascular Events
MFS	Metastatic free survival
mITT	Modified intent to treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

Abbreviation	Definition
NMA	Network Meta-Analysis
NR	Not reported
PICOD	Population, intervention, comparator(s), outcome(s) and study design(s).
PFS	Progression free survival
PSA	Prostate specific antigen
PrSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SUCRA	Surface Under the Cumulative Ranking Curve
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Overview of key issues

ID	Summary of issue	Report sections
Issue 1	Generalisability of evidence to high-risk localised HSPC	2.3, 4.2.3
Issue 2	Treatment effects on risks of MACE	3.4.3, 3.4.4, 4.2.6.2.4
Issue 3	Cost effectiveness for the spinal metastases subgroup	4.2.4, 5.4, 6.4

HSPC, hormone sensitive prostate cancer; MACE, major adverse cardiovascular events

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the assumption of a carry-over period for effect on risk of major adverse cardiovascular events (MACE); exclusion of enzalutamide for treatment of non-metastatic hormone sensitivity prostate cancer (HSPC) to reflect NICE guidance (TA580).

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reducing the incidence of major adverse cardiovascular events (MACE) relative to treatment with GnRH agonists
- Increasing life years due to a reduction in fatal MACE
- Improving health-related quality of life due to reduction non-fatal MACE

Overall, the technology is modelled to affect costs by:

- Increasing ADT costs
- Increasing subsequent treatment costs due to increased survival
- Reducing drug administration costs

The modelling assumptions that have the greatest effect on the ICER are:

- The source used to estimate the treatment effect on MACE incidence
- Subsequent treatment costs for castration-resistant prostate cancer
- The proportion of MACE events that are fatal

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Generalisability of evidence to high-risk localised HSPC

Report section	2.3, 4.2.3
Description of issue and why the EAG has identified it as important	The company submission does not report clinical or economic evidence specific to the recent licence extensions for use of relugolix to treat high-risk localised HSPC in combination with radiotherapy (adjuvant setting) or prior to radiotherapy (neoadjuvant setting). The company believe that the submission can be generalised to support these indications, as the licence extensions were based on the same HERO trial data presented in the CS (which includes a subgroup with high-risk localised HSPC). It is also noted that ADT as a pharmacological class is recommended by recent clinical guidelines to treat high-risk localised and locally advanced HSPC. The company also suggest that the effect of relugolix on MACE (the key driver of cost-effectiveness results) is unlikely to differ in this subgroup. We understand that treatment for people with high-risk localised HSPC and locally advanced HSPC is generally the same, but there is uncertainty over the magnitude of the effects. Differences in risks of disease progression and duration of treatment and costs in adjuvant and neoadjuvant settings might also affect cost-effectiveness.

What alternative approach has the EAG suggested?	We question whether evidence on the cost-effectiveness results from the base case model are generalisable to the licence extensions for high-risk localised HSPC in adjuvant and neoadjuvant settings.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Additional information from clinical trials or observational studies. Expert opinion on the plausibility of generalising clinical and economic evidence to the licence extensions for relugolix for high-risk localised HSPC.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Treatment effects on risks of major adverse cardiovascular events

Report section	3.4.3, 3.4.4, 4.2.6.2.4
Description of issue and why the EAG has identified it as important	There is uncertainty over the relative effects of relugolix and comparators on the incidence of MACE events, as estimates differ between sources and methods of analysis, including direct estimates from the HERO trial and pooled estimates from the company's network meta-analyses (NMAs) and from other published sources. These differences may be explained by the use of different definitions of MACE events, populations and drug doses. The EAG requested that data from the phase II trial of relugolix versus leuprolide (C27002 NCT02083185) should be included in the company's NMAs. In response, the company updated their NMA for the outcome of testosterone suppression, but they did not update the NMA for MACE incidence, stating that these data were not available. The EAG notes that the data are available in the clinical study report (CSR), and that the CSR was only obtained by the company itself during the clarification question stage of the appraisal. We also note that data on MACE incidence from study C27002 available in the trial's clinicaltrials.gov record were included in a published meta-analysis (Cirne et al.) (although this appears to have included data for the unlicensed 80 mg dose of relugolix.) This is a key issue because the relative effect of relugolix on the risk of MACE is the main driver of results from the company's economic model.
What alternative approach has the EAG suggested?	Pooled (NMA) estimates of effects on MACE incidence based on all relevant data (including C27002 and other relevant phase II studies).
What is the expected effect on the cost-effectiveness estimates?	The impact of estimated effects on MACE incidence is explored through company and EAG scenario analysis. If the effect of relugolix on reducing MACE incidence is removed from the model, relugolix is 'dominated' (more expensive and

	no more effective than comparators). Base case results are not very sensitive to estimates from different sources tested by the EAG, as the base case ICER is low. Results for the subgroup with spinal metastases are more sensitive, and the effect of degarelix on MACE incidence is also a factor in this subgroup.
What additional evidence or analyses might help to resolve this key issue?	Updated NMA including all available data relevant to the decision problem, with appropriate exploration of heterogeneity.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 3 Cost effectiveness for the spinal metastases subgroup

Report section	4.2.4, 5.4, 6.4
Description of issue and why the EAG has identified it as important	The company did not include degarelix as a comparator in their base case analysis because degarelix is only recommended in England for advanced HSPC in a subgroup of people with spinal metastases (NICE TA404). The NICE recommendation took into consideration the additional risks of spinal compression in this subgroup. The company therefore report cost-effectiveness results for relugolix in a subgroup of HSPC with spinal metastases, including degarelix as well as GnRH agonists as comparators. This subgroup analysis uses model assumptions and parameter estimates for all people with metastatic HSPC. The company states that estimation of the effects on MACE specific to people with spinal metastases would require analysis of a very narrow subpopulation. They consider that the broader metastatic subgroup is the best proxy for people with spinal metastases.
What alternative approach has the EAG suggested?	There is some uncertainty over estimates of cost-effectiveness for the subgroup of patients with spinal metastases based on model assumptions and parameters for the broader subgroup of people with metastatic HSPC.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Consideration of whether the cost-effectiveness of relugolix compared with degarelix and GnRH agonists is likely to be at least as good for people with HSPC with spinal metastases as for the broader group of all people with metastatic HSPC.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The cumulative effects of EAG corrections and preferred assumptions on the company's base case analysis are shown in Table 2. These results include a confidential patient access scheme (PAS) discount for relugolix, but other drugs are costed at non-confidential NHS

prices. We report results including all confidential discounts for comparator, concurrent or subsequent treatments in a confidential 'cPAS' addendum to this report.

Table 2 Cumulative effect of EAG changes to the company's base case analysis

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base case	[redacted]	[redacted]	10,751
EAG corrections	[redacted]	[redacted]	7,870
Exclude enzalutamide for nmCRPC	[redacted]	[redacted]	8,088
Prior MACE at baseline from HERO trial	[redacted]	[redacted]	8,364
End-of-life cost from Georghiou 2012	[redacted]	[redacted]	9,382
Exclude carry-over period for effect on MACE	[redacted]	[redacted]	9,990
EAG's preferred base case	[redacted]	[redacted]	9,990

Modelling errors identified and corrected by the EAG are described in 5.5.2. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.1.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Accord Healthcare on the clinical effectiveness and cost effectiveness of relugolix for treating treating hormone-sensitive prostate cancer. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 5th February 2024. A response from the company via NICE was received by the EAG on 26th February 2024 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on hormone sensitive prostate cancer

The company provided a comprehensive overview of the different stages of prostate cancer, its epidemiology treatment and disease burden in CS section B.1.3.

Prostate cancer is the most common cancer in males in the UK, with approximately 51,000 new cases diagnosed in England in 2022.[1] Age, ethnicity, family history of prostate cancer and obesity are the most significant risk factors for prostate cancer.[2] Prostate cancer can be classified into localised, locally-advanced and metastatic, depending on whether, and how far, the cancer has spread. Localised and locally advanced prostate cancer can be further classified according to risk of progression based on prostate-specific antigen (PSA) concentration, Gleason score and TNM (tumour, lymph node, metastasis) staging. Traditionally, there were 3 risk groups (low-risk, intermediate-risk, high-risk) however, healthcare professionals now divide localised and locally advanced prostate cancer into 5 risk groups according to the Cambridge Prognostic Group (CPG) model. The 5 risk groups range from CPG1 to CPG5. CPG1 aligns to the previous low-risk group, CPG2 and CPG3 to the previous intermediate-risk group and CPG4 and CPG5 to the previous high-risk group.[3]

Androgen deprivation therapy (ADT) is the term used to describe a group of surgical and hormonal drug treatments which collectively is one of the main forms of treatment for prostate cancer. However, ADT causes metabolic and cardiovascular adverse effects. Consequently the risk of cardiovascular disease is higher in patients with prostate cancer compared to the general population.[4 5] Clinical expert advice to the EAG, stated that the

current treatment to mitigate these adverse effects are lifestyle advice and regular monitoring of blood pressure and cholesterol levels. An androgen deprivation therapy without cardiovascular related adverse effects is therefore an unmet need.

2.2.2 Definitions of advanced prostate cancer

The scope of the current technology appraisal focuses on the population of patients with hormone sensitive prostate cancer (HSPC) (also known as hormone dependent prostate cancer). These are patients who are ADT naïve (i.e. who have not received ADT previously), or whose disease is continuing to respond to ADT. The CS focuses on a subgroup of this population, those with *advanced* hormone sensitive prostate cancer, which is in line with the marketing authorisation of relugolix. The NICE scope considers advanced prostate cancer to include **locally-advanced or metastatic disease**, including biochemical relapse (a rising PSA level after initial treatment). Clinical expert advice to the EAG is that advanced cancer usually refers to metastatic cancer. In the CS and subsequent company clarification response (A1), there is ambiguity as to what the company considers advanced prostate cancer to include.

- In CS section B.1.3.2, the company define advanced prostate cancer to encompass: **metastatic disease**, **locally advanced disease** (Stages T3-T4) and **advanced localised disease** (defined in the CS as "T1 or T2 and PSA between 10 - 20ng/ml and Gleason 3+4 or Gleason grade 4+3" with the citation of Moul 2004).[6]
- The EAG's examination of Moul (2004),[6] revealed that the company's definition is inconsistent with the Moul publication, which states *"Patients categorized as having "high risk" localized disease (Table 1) have PSA levels above 20 ng/mL or a Gleason score ≥8, or the 1992 American Joint Committee on Cancer tumor stage T2c or T3. These patients, particularly the younger men, could now be defined as advanced prostate cancer patients because of their increased risk for death from the disease, even though it is detected at a localized stage."*
- The EAG therefore asked the company to clarify whether the definition of advanced prostate cancer in the CS is correct, in particular the definition of advanced localised disease (clarification question A1). In their response the company acknowledge that it is incorrect and that the text should read: *"The definition has been expanded to encompass patients with significant risk of disease progression and/or death, using stage, Gleason grade and PSA level e.g. locally advanced disease (stages T3-T4) and advanced localised disease (defined as PSA above 20ng/ml and Gleason score ≥ 8)."*

- Clinical expert advice to the EAG is that the definitions provided by the company in the CS and in their clarification response (in respect to advanced localised disease and CPG stage 2 locally advanced disease) are actually referring to intermediate-risk localised disease instead. Furthermore, the expert commented that high-risk localised disease should be defined as CPG 4 or 5, with high PSA, Gleason score ≥8 and T2 or features of T3 or N1.
- The EAG clinical expert also advised that intermediate-risk localised disease, high-risk localised disease and locally advanced disease are managed similarly in clinical practice, which aligns with the treatment algorithms in NG131.[3]
- The company cite NICE clinical guideline 131 (NG131) which recommends to "Offer people with CPG 2, 3, 4 and 5 localised or locally advanced prostate cancer 6 months of androgen deprivation therapy before, during or after radical external beam radiotherapy", and to "Consider continuing androgen deprivation therapy for up to 3 years for people with CPG 4 and 5 localised or locally advanced prostate cancer, and discuss the benefits and risks of this option with them". The company go on to state that “CPG stage 2 locally advanced within the NICE guidelines is aligned with our company submission definition (Gleason score 3 + 4 = 7 (grade group 2) or PSA 10 microgram/litre to 20 microgram/litre and Stages T1–T2).”
- The upshot of the above is that the company appears to propose that relugolix should be considered for use in the same population as NG131 recommends should receive ADT, which includes intermediate risk localised disease. The EAG notes that GnRH agonists are recommended by NICE in NG131 for intermediate-risk localised disease, which is outside of their licensed indications. Intermediate-risk HSPC patients are not included in the relugolix marketing authorisation (see below section 2.2.3 for details of the label). Additional expert clinical advice on this issue may provide further clarification on the definitions relating to advanced prostate cancer.

2.2.3 Background information on relugolix

CS Section B.1.2. describes the mechanism of action of relugolix. Briefly, relugolix is a non-peptide gonadotrophin-releasing hormone (GnRH) receptor antagonist. It competitively binds to the GnRH receptors in the anterior pituitary preventing native GnRH from binding and signalling the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This results in the testes producing less testosterone. The current technology appraisal assesses the clinical and cost-effectiveness of relugolix (Orgovyx™) in the context of its current marketing authorisation:

- For the treatment of adult patients with advanced hormone-sensitive prostate cancer (initial licensed indication).
- For the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy (approved in a recent license variation submission by MHRA in December 2023).
- As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer (approved in recent variation submission by MHRA December 2023).
-

The recommended dose for relugolix is an initial loading dose of 360 mg (three tablets) on the first day of treatment, followed by a 120 mg (one tablet) dose taken once daily (QD) at approximately the same time each day thereafter.

2.2.4 The position of relugolix in the treatment pathway

Hormone sensitive prostate cancer requires androgens, including testosterone, to grow. Hormone therapy can inhibit the growth of prostate cancer. The most used hormone therapy for prostate cancer is ADT, which reduces androgen production in the testicles. ADT includes surgery to remove both testicles (orchidectomy) and drug treatment in the form of gonadotrophin-releasing hormone (GnRH) agonists (as also known as lutenising hormone releasing hormone (LHRH) agonists) or GnRH antagonists (also known as LHRH antagonists). These are briefly described below.

Surgery (orchidectomy): NG131 recommends bilateral orchidectomy as an alternative to continuous GnRH agonist therapy to all people with hormone naïve metastatic prostate cancer.

GnRH agonists: These include leuprorelin, triptorelin, goserelin, buserelin. Clinicians consider each GnRH agonist to have equivalent clinical efficacy.[7] Clinical expert advice to the EAG notes that all GnRH agonists are administered in the form of depot injections for prostate cancer, and that buserelin is rarely used in clinical practice. The EAG notes that GnRH agonists are recommended by NICE in NG131 for intermediate-risk localised disease,[3] which is outside of their licensed indications.[8-11] Limitations of GnRH agonists include:

- Injection site reactions and handling errors in preparation and administration.
- A surge in testosterone (known as a “testosterone flare”) lasting 1 to 3 weeks which can worsen prostate cancer symptoms such as bone pain and spinal cord

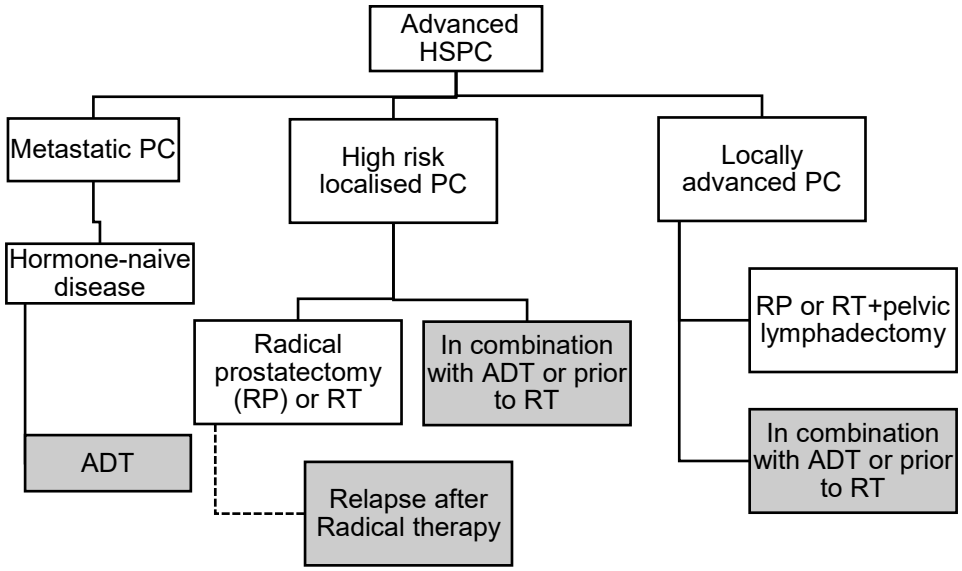
compression and may require treatment with antiandrogens e.g. (e.g., bicalutamide, flutamide, nilutamide);

- Increased risk of cardiovascular events compared to GnRH antagonists or bilateral orchidectomy, particularly in those with pre-existing cardiovascular disease. Clinical expert advice to the EAG is that this risk can only currently be managed by lifestyle advice and regular monitoring of blood pressure and cholesterol;
- Slow recovery of testosterone after discontinuation of treatment which can last for months prolonging the risks associated with treatment, including those associated with low testosterone levels. The EAG clinical expert highlighted increased insulin resistance and loss of bone density as risks of particular concern.

GnRH antagonists: Degarelix is currently the only GnRH antagonist recommended for use in England. Its use is limited to patients who have advanced hormone sensitive prostate cancer with spinal metastases (TA404).[7] As with GnRH agonists, degarelix is also administered via a long acting injection (once a month). A benefit of degarelix compared to GnRH agonists is that it does not cause a testosterone flare. Limitations of degarelix include:

- a higher rate of injection site reactions compared to GnRH agonists (e.g. 44% compared to <1 with leuprolide).
- A slow recovery of testosterone after discontinuation of treatment.

CS section B.1.3.9 and CS Figure 1 present the position of relugolix in the treatment pathway. The EAG considers CS Figure 1 to be unclear and asked for the company for clarification. The company presented a revised version of CS figure 1 in company clarification response A2 figure 1, which is presented below in Figure 1



Relugolix is indicated (highlighted in grey shading) for patients with high-risk localised, locally advanced, metastatic hormone-sensitive disease who would otherwise have ADT. Relugolix is also indicated for patients who relapse after radical treatment (broken line). Adapted from NICE treatment recommendations for advanced prostate cancer (NG131)[3] and ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[12]
Source: Reproduced from CS clarification question response A2 Figure 1.

Figure 1 NICE pathway for the management of advanced hormone-sensitive prostate cancer

The footnote to the above figure indicates that relugolix is in the same position as other ADTs for the treatment of high-risk localised, locally advanced, and metastatic hormone-sensitive disease according NG131 and ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[3] [12] Given this, and the information provided in company clarification response A1, the EAG interpret the company's position of relugolix in the care pathway as:

- before (i.e. **neoadjuvant**) during or up to three years after (i.e**. adjuvant**) treatment with radiotherapy in patients with **intermediate or high-risk localised** disease **or locally advanced disease**. The EAG note that **intermediate-risk localised disease** is not included in the licensed indications for relugolix; however the EAG clinical expert commented that intermediate-risk and high-risk localised disease and locally advanced disease are treated in a similar manner clinically. The EAG expert also reiterated that, as per NG131, hormone therapies should not be used in conjunction with prostatectomy.

- treatment for patients with **biochemical relapse** if there is evidence of symptomatic local disease progression or any proven metastases or a PSA doubling time of less than 3 months.
- first line treatment of **metastatic HSPC**, alone or in the following combination with docetaxel, docetaxel plus darolutamide (TA903),[13] enzalutamide (TA712),[14] or with apalutamide if docetaxel is unsuitable (TA741)[15]

The EAG's interpretation of the position of relugolix is illustrated below in Figure 2.

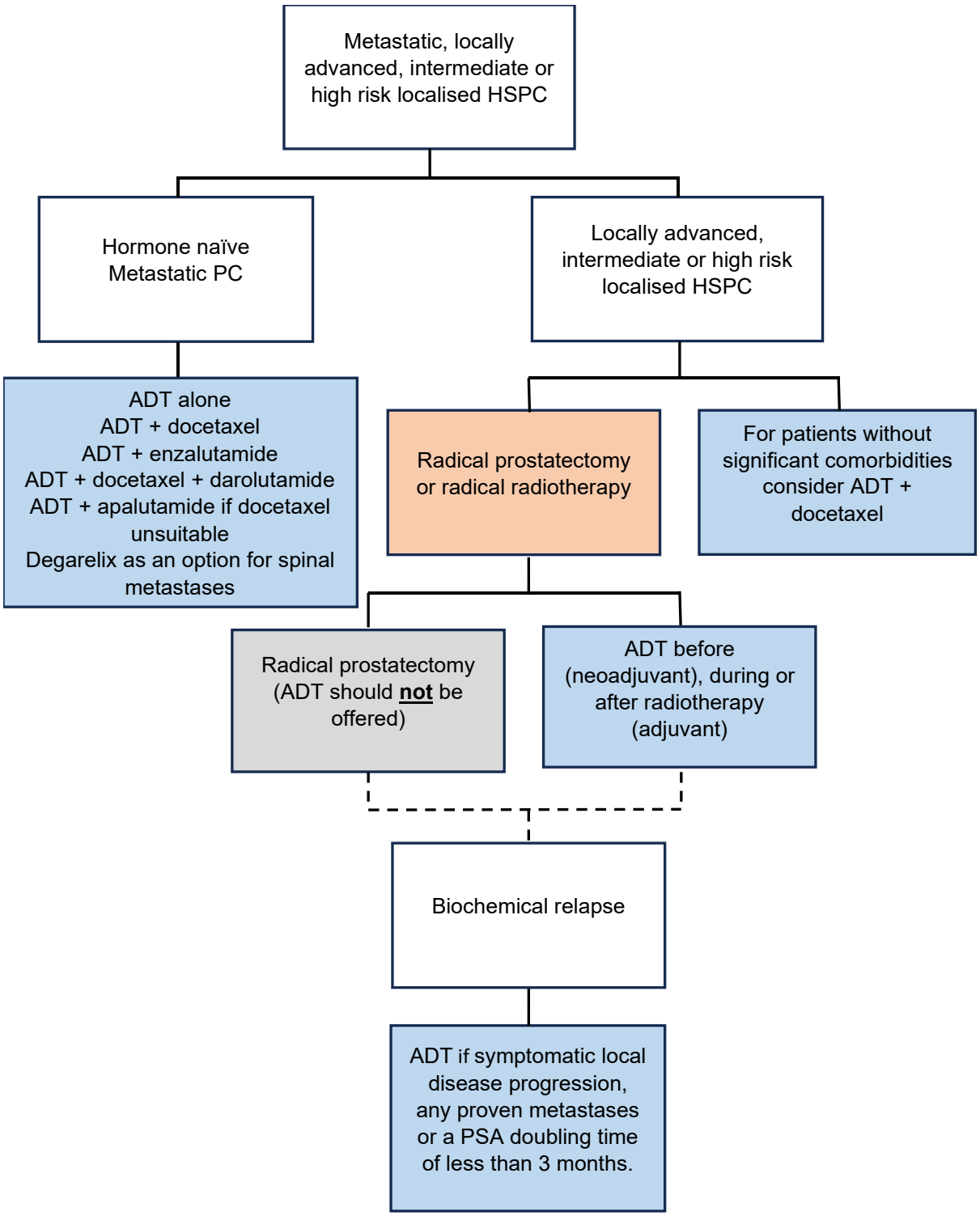


Figure 2 EAG interpretation of the company's position of relugolix in the hormone sensitive prostate cancer care pathway

Source: Partly reproduced from CS clarification question response A2 Figure 1. Based on NICE treatment recommendations in NG131,[3] TA404,[7] TA712,[14] TA741[15] and TA903[16]
Abbreviations: ADT, androgen deprivation therapy; HSPC, hormone sensitive prostate cancer; PC, prostate cancer. White boxes: relevant indications for ADT, including relugolix; Orange box: key clinical decision; Grey box: ADT, including relugolix, not recommended; Blue boxes: treatments incorporating ADT currently recommended by NICE

2.3 Critique of the company's definition of the decision problem

Table 3 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this.

Table 3 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	People with hormone-sensitive prostate cancer	CS Table 1 states *"People with hormone-sensitive prostate cancer"* but data presented in the CS is for people with advanced hormone-sensitive prostate cancer (defined in the CS as high-risk localised, locally advanced or metastatic, including biochemical relapse).	Not stated	Data presented in the CS is in line with the original license for relugolix i.e. *"For the treatment of adult patients with advanced hormone-sensitive prostate cancer"* (CS Appendix C). The EAG note the company consider advanced prostate cancer to include high-risk localised disease. The EAG interpret information provided in company clarification response A1 implies the company wish relugolix to be considered for patients with intermediate-risk localised disease, which is outside of licensed

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
				indications. Clinical expert advice to the EAG is that intermediate-risk and high-risk localised disease is treated in a similar manner to locally advanced disease. The EAG consider the population presented in the C*S* to be synonymous with subgroup 1 of the NICE final scope (i.e. People with advanced hormone-sensitive prostate cancer (locally advanced or metastatic, including biochemical relapse).
Intervention	Relugolix	As per final scope	Not applicable	As per final scope
Comparators	Androgen deprivation therapy alone (including orchidectomy, GnRH agonists such as leuprorelin, goserelin, triptorelin, and buserelin, and GnRH antagonists such as degarelix)	As per final scope	Not applicable	As per final scope

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • prostate-specific antigen response • time to prostate-specific antigen progression • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • overall survival • response rate (testosterone suppression) • prostate-specific antigen response • time to prostate-specific antigen progression • adverse effects of treatment • health-related quality of life. • Major cardiovascular events • testosterone recovery CS section B1.1 Table 1 states progression free survival is considered an outcome; however this is not explicitly reported in the CS. Castration resistance free	The company included 2 additional outcomes: major cardiovascular events (MACE) and testosterone recovery. A detailed rationale for the inclusion of these two outcomes, is presented in CS Table 1. .	The EAG considers all outcomes with the exception of progression-free survival, MACE and testosterone recovery as per final scope. The EAG considers these outcomes are appropriate for consideration in the appraisal.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
		survival, however is reported in CS section B.2.6.1.10.b. Events for this outcome are due to PSA progression or due to on-treatment death		
Subgroups	• Subgroup 1: People with advanced hormone-sensitive prostate cancer (locally advanced or metastatic, including biochemical relapse) • Subgroup 2: People with high-risk localised or locally advanced hormone sensitive prostate cancer in combination with radiotherapy • Subgroup 3: People with high-risk localised or locally advanced hormone sensitive	Subgroup 1: People with advanced hormone-sensitive prostate cancer (**high-risk localised**, locally advanced or metastatic, including biochemical relapse) The company do not present any separate data for subgroups 2 and 3.	Subgroup 1: The company consider advanced prostate cancer to additionally include high-risk localised disease and cite Moul, 2004. Subgroups 2 and 3: The company considers these groups to be "supported by the same dataset as	Subgroup 1: Clinical expert advice to the EAG is that high-risk localised disease is treated in an identical manner to locally advanced disease. The EAG consider the population presented in the company submission to be synonymous with subgroup 1 of the NICE final scope. Subgroup 2: The EAG note that an approved indication for relugolix is "*People with high-risk localised or locally advanced hormone sensitive prostate cancer in combination with*

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	prostate cancer requiring neoadjuvant treatment prior to radiotherapy		the original license population, as these patients comprise a subset of patients in the HERO study for which there were no pre-specified analyses." (CS Table 1)	*radiotherapy",* which aligns with subgroup 2 in the NICE final scope Subgroup 3: The EAG note that an approved indication for relugolix is "As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer", which aligns with subgroup 3 in the final scope.

Source: CS Table 1

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS includes a systematic literature review (SLR) of the clinical efffectiveness of relugolix as a treatment for advanced prostate cancer (CS Appendix D). The primary purpose of the SLR was "*to address the specific research question*"; the EAG could not find an explicit research question stated in the CS, but we assume this is a reference to the decision problem and the NICE scope, the overall remit of which is to assess the clinical effectiveness and cost effectiveness of relugolix within its marketing authorisation for treating hormone-sensitive prostate cancer. A secondary objective of the SLR was to identify evidence appropriate for consideration in an indirect treatment comparison (ITC) to relugolix.

The SLR presented in the CS is an update of an SLR originally conducted in March 2020 and updated periodically since then to identify evidence for the safety and efficacy of treatments for HSPC.

Appendix 1 of this EAG report provides a summary of the EAG's critical appraisal of the company's systematic review (Table 44). Overall, the EAG considers that the review was conducted appropriately, but we note some uncertainties in the following areas:

- The literature searches were nine months out of date when the EAG received the CS, and it is possible that relevant studies may have been published during this period. The EAG did not, however, run an update of the search.
- Limited details are presented for one of the trials identified by the SLR, a phase II RCT comparing relugolix against leuprolide (Study C27002, NCT02083185). In response to a clarification question (A9) the company stated that "*access to the full dataset was limited at the time of submission".* In addition, they state that their view that trial gives no additional support for the use of relugolix since a phase III RCT (the HERO trial) published its results. We discuss this issue further in section 3.2.1, and section 3.3 of this report.
- The company appears to have applied the critical appraisal instrument (Cochrane risk of Bias version 2) to studies included in the NMA incorrrectly. The instrument is designed to allow multiple risk assessments of a given study, to reflect the fact that risk of bias can vary between different outcome measures within the same study. Instead, the company reports one overall risk of bias judgement per study, without explaining which study outcome(s) (result) the bias judgement is based on. For this

reason the EAG urges caution in the interpretation of the company's risk of bias judgements as these are currently unclear.

- The CS mentions that "*an observational studies SLR with the corresponding research question and objective was also undertaken, to identify all supporting evidence for the treatment of hormone-sensitive, advanced prostate cancer*" (Appendix D1.1, page 27). However, we could find no further details in the CS of this review.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The SLR identified 54 publications featuring 38 unique trials which were data extracted and assessed for methodological quality. Studies were categorised into one of three sub-groups based on the status of the comparator treatment (Table 4).

Table 4 Categories of study identified by the SLR

No. studies	Category	Summary description
7	ADT of interest[a] vs ADT of interest	Phase I-III trials and an observational study of relugolix for HSPC
24	ADT of interest[a] vs other therapy	RCTs of relugolix and other ADT treatments, or other (non-ADT) therapies for potential inclusion in an NMA
7	ADT open label extension studies	

[a] 'Of interest' means it is relevant to the company's decision problem

The seven unique trials in the ADT of interest vs ADT of interest grouping include a pivotal phase III RCT of relugolix versus leuprolide (the **HERO** trial) and two phase II trials comparing relugolix with leuprolide (**C27002**, NCT02083185, also inconsistently referred to as CTgov 2018 in the CS) or with degarelix (**C27003** NCT02135445). Of these, the pivotal phase III RCT (**HERO**) and one of the phase II trials (**C27003** NCT02135445) are presented in the most detail in the CS.

As mentioned earlier (section 3.1), one of the explanations the company gave regarding why few details of study **C27002** (NCT02083185) are provided in the CS is because it is published only in conference abstract form.

- The EAG notes that the clinicaltrials.gov record for this study reports detailed study information including efficacy and safety results (webpage last accessed 20th March 2024). The CS cites the clinicaltrials.gov record.
- The company also mentioned that access to the full trial dataset was "limited" at the time of the submission. The dataset is owned by the trial sponsor, Myovant Sciences (now Sumitomo Pharma Co.) (NB. The original development of relugolix was done by Takeda Pharmaceuticals, and subsequently relugolix was licensed to Myovant Sciences before being licensed by Accord). The company were able to acquire the CSR from the sponsor at the request of the EAG (clarification question A6) stating that this *"has been provided to Accord once context regarding the clarification questions was given".*
- Another explanation offered for the lack of detail on study C27002 is because the company, "*does not believe that NCT02083185 provides any additional support for the use of relugolix beyond the evidence given in the HERO trial, since both trials assess relugolix against the same comparator (leuprolide) in the same patient population*" (company response to clarification question A9). The EAG, however, doesn't share the company's opinion.
- The fact that both studies compared relugolix 120mg to leuprorelin for 48 weeks and report similar outcome measures lends support to combining them in a meta-analysis. This would increase the total sample size and give greater precision to the effect estimates.
- It would be particularly informative to include both HERO and C27002 studies in a network meta analysis comparing relugolix with other ADTs. Certainty and precision in the results of NMA are likely to improve as evidence accumulates, hence *"A network meta-analysis exploits all available direct and indirect evidence"* (Chaimani et al, 2023). [17] It would be informative to observe the degree to which the clinical effectiveness and safety results are consistent between the two trials, amongst other things.

The remaining four (ADT of interest vs ADT of interest) studies comprise two phase I dose finding (**TB-AK160108**, NCT02141659) / dose escalation (**C27001**, EudraCT 2011-002868-24) studies, a small phase II RCT (**Apa-RP** study, NCT04523207) and a retrospective real world evaluation of compliance with relugolix (The CS cites a publication in The Oncologist in relation to this study, reference number 94. However, reference 94 in the bibliography is a different study. The EAG has not been able to locate the correct citation for this study, however the company has since confirmed that the citation should refer to 90. Kasparian et

al, 2023). A brief narrative summary of each of these four studies is provided in CS Appendix D1.1 ('Other studies of relugolix').

The inclusion status of these studies in the CS and its respective components (i.e. the SLR, NMA, economic model) is not always clearly reported and easy to follow, and in some instances appears contradictory. For example, the company state that study **C27003** (NCT02135445), which compared relugolix to degarelix, is "excluded from the SLR" because the study population doesn't include those with advanced prostate cancer (the population is locally intermediate prostate cancer). Even though it is officially excluded from the SLR, the CS describes the methods and results of this study in a level of detail similar to that given to the pivotal phase III **HERO** RCT. The company's justification for presenting this detail is that it provdes data for the efficacy and safety of relugolix in combination with radiation therapy, as submitted in their application for a marketing authorisation variation (which was in progress at the time the CS was written). To provide a simplified overview of the evidence featured in the CS, the EAG has tabulated brief details of the seven studies (Table 5). As can be seen, the HERO RCT is the main source of clinical effectiveness evidence which informs the economic model.

Table 5 Studies of relugolix compared to other ADT treatments identified by the SLR

Study ID, design, sample size	**Intervention, comparator, population group**	**Included in:**		
		CS/ SLR?	NMA?	Model?
HERO (NCT03085095). Multinational Phase III, open-label, parallel group RCT.[18] N=934	Relugolix versus leuprolide in advanced prostate cancer	Yes/Yes	Yes	Yes
C27002 (NCT02083185) Proof of concept, dose-finding, randomized, open-label, parallel group phase II study N=134	Relugolix versus leuprolide in locally advanced or metastatic prostate cancer. (biochemical relapse, newly diagnosed or advanced localized disease unsuitable for immediate curative intent)	No/Yes[a]	No[b]	No

C27003 (NCT02135445) Phase II N=103	Relugolix versus degarelix in localised intermediate-risk prostate cancer	Yes/No[c]	No	No
TB-AK160108 (NCT02141659) Open-label, dose finding, phase I study N=43	Tolerability, safety, pharmacokinetics and pharmacodynamics of relugolix in hormone treatment-naïve Japanese patients with non-metastatic prostate cancer.	No/Yes[d]	No	No
C27001 (EudraCT 2011002868-24) Three-part, randomised, double-blind, placebo-controlled, phase 1 dose-escalation study N=176	Relugolix, in healthy male volunteers.	No/Yes[d]	No	No
Apa-RP study (NCT04523207) Single-arm, open label, multicentre, phase II study N=12	*Apa-RP sub study*: relugolix monotherapy for 2 weeks Apa-RP main study: Apalutamide + ADT (relugolix) for 28 days Patients with high-risk localised prostate cancer following radical prostatectomy	No/Yes[d]	No	No
Retrospective study Evaluation of compliance and efficacy in a real-world setting N=91	Relugolix prescribed for all ADT indications in prostate cancer	No/Yes[d]	No	No

[a]. Officially included in the SLR but only a brief narrative summary is provided in CS Appendix D1. Further detail on this study was provided to the EAG in response to a clarification question (A9)
[b]. Not originally included in the NMA but added in response to EAG clarification question A11
[c]. Excluded from the SLR but described in detail in the clinical effectiveness section of the CS.
[d]. Not included in the SLR but a brief narrative summary is provided in CS Appendix D1.1

In the following sections we focus mainly on the characteristics the **HERO** trial given its pivotal role informing the original relugolix licence award and its inclusion in the company's economic evaluation as a source of clinical effectiveness model parameters.

3.2.1.1 Study characteristics

A detailed description of the characteristics of the HERO trial is provided in CS sections B2.2 to B2.8. At the EAG's request (clarification question A5) the company provided the HERO trial protocol and statistical analysis plan, the HERO trial final analysis clinical study report (CSR), and specific data listings tables, figures and graphs referred to in the CSR but not included within the CS dossier (NB. The company was not able to obtain from the trial sponsor all the figures and tables we requested). All of these documents have company 'data on file' status. The main findings of the trial were published in the New England Journal of Medicine (Shore et al, 2020).[18] Below is a summary of the HERO trial methodology.

- **Objective.** To evaluate the safety and efficacy of oral relugolix compared to leuprolide
- **Intervention and comparator.** Relugolix (120 mg once daily after a single oral loading dose of 360 mg) versus leuprolide acetate (22.5 mg [or 11.25 mg in Japan and Taiwan] by injection every 3 months) for 48 weeks.
- **Included population**. Included men aged 18 or older with androgen-sensitive advanced prostate cancer who were candidates for at least 1 year of continuous ADT for the management of androgen-sensitive advanced prostate cancer and who were not candidates for surgical or radiation therapy with curative intent. Eligible participants included those with:
  - evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent (e.g. surgery, radiation therapy), or
  - newly diagnosed with androgen sensitive metastatic disease, or
  - advanced localised disease unlikely to be cured by local primary intervention with either surgery or radiation.
- **Excluded population.** Patients receiving ADT adjuvant or neoadjuvant to radiotherapy as primary definitive therapy. Also excluded were patients with MACE within 6 months before trial initiation.
- **Primary outcome.** The primary outcome was the sustained castration rate, defined as the cumulative probability of testosterone suppression to < 50 ng/dL from week 5, Day 1 (Day 29) through Week 49, Day 1 (Day 337). This outcome informs the economic model (see 4.2.6.1).

- **Secondary outcomes informing the economic model:** time to PSA progression (4.2.6.3), and adverse events including MACE (4.2.6.2.2).
- **Other secondary outcomes:** Testosterone suppression to <50 ng/dL (non-inferiority with respect to the primary outcome); PSA response, profound castration rate (<20 ng/dL), follicle-stimulating hormone (FSH) levels, castration resistant-free survival (CRFS), testosterone recovery, sustained profound castration rate, adverse events, overall survival, quality of life.
- **Study duration.** An initial screening period of 28 days, then a treatment period of 48 weeks and a follow-up period of 30 days. A subset of patients was followed up to 90 days to assess testosterone recovery.
- **Location.** 160 centres globally, including North and South America, Europe, and Asia Pacific region. European participating centres were located in, Austria, Belgium, Germany, Denmark, Spain, Finland, France, UK, Italy, Netherlands, Poland, Slovakia, and Sweden and accounted for 39.7% of the trial population (n=10 (1.1%) of the population were from the 4 UK study sites).

3.2.1.2 Patients' baseline characteristics

The HERO trial baseline characteristics are presented in CS section B.2.3.2.1 (demographic characteristics in CS Table 7, disease specific characteristics in CS Table 8). In brief, the mean and median age of participants was 71 years; the largest racial group was White (68%) followed by Asian (21%). In terms of clinical disease state at presentation, half of the population (50%) had biochemical or clinical relapse following local primary intervention with curative intent, followed by 27% with advanced localised disease not suitable for local primary intervention and 23% with newly diagnosed androgen-sensitive metastatic disease. The vast majority had an ECOG cancer performance status score of 0 (88%), which indicates that a person is fully active and unrestricted in their ability to work or self care. In terms of Gleason score, the largest proportion (43%) scored 8, indicating the cancer is likely to grow quicky, whilst the second largest proportion (39%) scored 7, indicating likely moderate growth of cancer cells. Just over 90% of the trial population had at least one cardiovascular risk factor from the three main risk categories assessed (lifestyle risk factors, cardiovascular risk factors, and history of a major adverse cardiovascular event).

The CS (section B.2.3.2) reports the distribution of patient baseline characteristics across the randomised treatment arms of the HERO trial and concludes that they are similar and representative of the intended target population for this study, as well as for patients with advanced prostate cancer in general. The EAG agrees with the company that baseline characteristics are similar, though we note that the mean PSA level at baseline was higher in

the relugolix arm (104.2 ng/mL) than in the leuprolide arm (68.6 ng/mL). However, the median PSA values were more comparable between the two arms (11.7 and 9.4 ng/mL, respectively) which suggests that the mean values may have been skewed by the occurrence of outliers.

EAG comment on included studies

The **main source of clinical effectiveness evidence for relugolix in the company submission is from the pivotal phase III trial (the HERO trial) which compared relugolix versus leuprolide. This trial supported the regulatory approval of relugolix and informs the economic evaluation in the CS. Also relevant are the phase II trials comparing relugolix with leuprolide (C27002)) or with degarelix (C27003).**

3.2.2 Risk of bias assessment

The HERO trial was critically appraised in the CS based on the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in healthcare (CS Table 12). The CS refers to this exercise as an assessment of study quality rather than risk of bias (except in CS Appendix D, where Cochrane risk of bias criteria were applied to studies under consideration for inclusion in an NMA – see sections 3.3 and 3.4 of this report). The EAG notes that the CRD instrument was not necessarily intended to elicit low or high risk of bias judgements, but nonetheless most of the questions do relate to a given bias domain. For example, the first two questions (randomisation and concealment of allocation) both address the risk of selection bias. That is, bias due to differences in patient characteristics between trial arms at baseline which can arise if allocation of participants to trial arms is not truly random or if knowledge of the randomisation sequence provides an opportunity to subvert the random allocation process.

Table 6 reports the results of the company's critical appraisal of the HERO trial. For comparison, we have added the EAG's own independent critical appraisal of those studies alongside those of the company. The company did not report a critical appraisal of study C27002.

Table 6 Critical appraisal of trial methodology by the company and the EAG

Criteria	HERO study	
	CS	EAG
1. Was randomisation carried out appropriately?	Yes	Yes

Criteria	HERO study	
	CS	EAG
2. Was the concealment of treatment allocation adequate?	Yes	Yes
3. Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
4. Were the care providers, participants and outcome assessors blind to treatment allocation?	Open label. Outcome assessors blinded	No, No, Yes
5. Were there any unexpected imbalances in drop-outs between groups?	No	No
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes (mITT), Yes, Yes

Source: Partly reproduced from CS Table 12.
mITT, modified intention to treat

As Table 6 shows, the EAG's responses to the questions were similar to the company's, indicating agreement that the HERO trial is at low risk of bais generally. Of note, whilst the EAG and the company agreed that randomisation was carried out appropriately (question 1), precise details of the method of generating the randomisation sequence were not provided in the CS or the trial journal publication. The EAG examined the trial CSRs but found that the information we required was located in a separate appendix which the company failed to provide with the CSR itself. We were therefore unable to independently verify if the method used was truly random. From the information that is available we noted that patient enrolment into the trial was facilitated by use of an interactive voice/web recognition system. Such systems have become increasingly common in clinical trials to manage the entry of new participants into a trial, in an efficient and systematic manner. These computerised interactive systems can perform many functions including the ability to generate random number sequences for allocating participants to study groups.[19] The EAG has therefore made the reasonable assumption that in the HERO trial automated computer randomisation was used to randomly allocate participants to the respective trial arms.

The EAG notes that the HERO trial underwent a second critical appraisal based on the Cochrane Risk of Bias tool version 2, as part of a feasibility exercise for the NMA (see section 3.3.4). Contradictorily, the randomisation was flagged as having 'some concerns' (CS Figure 28) in the Cochrane risk of bias assessment, due to insufficient available details about the randomization process. This is inconsistent with the company's own judgement (plus that of the EAG) based on the CRD criteria.

In relation to blinding, the CS mentions that HERO was an open-label trial with data access restrictions to minimise bias. The statistician responsible for writing the statistical analysis plan was blinded to treatment allocation, as was a programmer (no further information is given about the role of the programmer and how this relates to outcome assessment). The rest of the statistical analysis plan study team were unblinded. Furthermore, the trial journal publication reports that testosterone values for the primary end-point analysis were measured at a blinded central laboratory. The EAG's interpretation of the above information is that blinding procedures were in place for outcome assessors in relation to the primary outcome, though it is unclear whether such procedures applied to all outcome measures in the trial.

With regard to the final item in Table 6, a three part question about the trial analysis population, the company's response was a single 'Yes'. The EAG interprets this response to mean the trial did include an ITT analysis and that they consider this to be appropriately implemented and that they consider methods used to account for missing data were appropriate. The EAG's response to this item is: 'Yes' the analysis is what's known as a modified ITT (mITT) analysis (the term mITT is explicitly stated through the CS); and 'Yes' this was appropriate. The mITT population was defined as all randomised patients who received at least one dose of any study drug. Given that 99.7% and 99.4% of the randomised patients in the relugolix and leuprolide trial arms respectively were classed as 'treated' (we assume this means they received at least one dose of the study drug) the mITT population can be seen as comparable to the 'true' ITT population in terms of size (i.e. all randomised patients).

EAG comment on risk of bias in the HERO trial

The company and the EAG's critical appraisal judgements of the HERO trial agree that overall the trial is at low risk of bias (notwithstanding the fact that it is an open-label trial).

We discuss the company's risk of bias assessment of the trials considered for inclusion in the NMA later in this report in section 3.3.4.

3.2.3 Statistical methods of the HERO trial

Table 7 gives an overview of the statistical methods of the HERO trial. In general the methods used are appropriate for a phase III clinical trial, using standard assumptions and tests. The trial used a modified intention to treat (mITT) analysis which included all but four of the randomised population, thus minimising the impact of post randomisation exclusions. A pre-specified fixed-sequence hierarchical testing procedure for the primary outcome and key secondary outcomes prevented the probability of detecting "false positive" statistically significant findings (type I error). The statistical power calculation was designed to enable the trial to assess both the superiority and non-inferiority of relugolix to leuprolide for the primary outcome. The trial recruited a sufficient number of participants to fulfil the power calculation. The statistical analysis was designed to meet the requirements of pharmaceutical regulators in the US and in Europe, thereby giving confidence that the approach taken was sound.

Table 7 Overview of statistical analyses in the HERO trial

Analysis populations		
mITT population: all randomised patients who received at least one dose of any study drug. Primary: 930/934 (99.6%) Final: 1074/1078 (99.6%) Final metastatic mITT n=434 (40.3%)	**Per-protocol:** those from the mITT population with no important protocol deviations. Used for sensitivity analysis for the primary outcome. Primary: 864/934 (92.5%)	**Safety population:** all randomised patients who received at least one dose of the study drug. Based on the actual treatment received. Primary population for safety analyses. Primary: 930/934 (99.6%) Final: 1074/1078 (99.6%) Final metastatic safety n=434 (40.3%)
EAG comment: No concerns with the mITT population. Only a minority of randomised patients (n=4, two from each trial arm) not included in the mITT analysis, therefore any impact of exclusions would be negligible. Per protocol and safety populations have standard definitions and are analysed appropriately.		
Sample size calculations		

Based on the assumptions that the probability of sustained testosterone suppression was 94% and 96% for relugolix and leuprolide, respectively, with a 2:1 randomization ratio (relugolix: leuprolide); and dropout rate of 15%. With a non-inferiority margin of -10% and an overall two-sided type I error rate of 0.05 approximately 915 patients (610 relugolix, 305 leuprolide) were needed for at least 99% power to declare the non-inferiority of relugolix to leuprolide at the primary analysis.
EAG comment: The sample size calculations are appropriate for the purposes of demonstrating non-inferirority. The trial exceeded its target sample size at the primary analysis (n=934 recruited, n=915 target).
Methods to account for multiplicity
A pre-specified fixed-sequence hierarchical testing procedure was implemented to maintain the overall familywise error rate of 0.05 for the testing of primary and key secondary endpoints. If the primary outcome was statistically significant then the key secondary outcomes were tested one by one in sequence. 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 was less than 0.05.
EAG comment: The fixed-sequence testing procedure used in the HERO trial is appropriate to avoid the probability of detecting “false positive” statistically significant findings (type I error) in trials with many outcome measures.
Analysis of outcomes
The primary outcome was evaluated using the Kaplan Meier method. For the primary outcome the noninferiority margin was −10 percentage points. If noninferiority was demonstrated, testing for statistical superiority was performed using the same 95% CI without multiplicity adjustments.
EAG comment: The methods used are appropriate to the outcomes measured.
Handling of missing data
For observed data analyses, missing data was not imputed and only observed records were included. Patients who missed two or more consecutive visits after week 5 day 1 or discontinued from the study early were considered to have an event at the target day of the earliest missed visit. Data for patients who discontinued treatment before a testosterone level ≥50 ng/dL was observed were censored at the last testosterone assessment before discontinuation
EAG comment: The EAG has no substantive concerns.
Sensitivity & post-hoc analyses

Four sets of sensitivity analyses of the primary outcome were done: (i) per protocol population; (ii) excluding patients receiving concomitant medications and herbal supplements; (iii) patients who had missed two or more consecutive visits after Week 5 Day 1 or discontinued early (iv) the impact of delayed testosterone suppression to castrate levels. CS Table 6 mentions “A pre-specified post hoc analysis” of the incidence of cardiovascular events in patients with or without a reported medical history of adverse cardiovascular events (patients with and without MACE) was performed.
EAG comment: The sensitivity analyses are comprehensive.

3.2.3.1 Outcome testing

Safety and efficacy outcomes were assessed at two analysis milestones: the primary analysis and the final analysis.

The **primary analysis** of safety and efficacy occurred after 934 patients were randomised to the study and completed the 48-week treatment period and 30-day safety follow-up visit or discontinued early. The majority of the trial results reported in the CS are from the primary analysis. The main HERO journal publication, published in May 2020, reports the primary analysis results (Shore et al. 2020).[18]

The **final analysis** 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.

Table 8 lists the outcome measures in the trial, classified as primary, key secondary, other secondary, exploratory efficacy, patient-reported and safety outcomes. (Definitions of these outcomes are given in CS B.2.4.1 and summarised in section 3.2.4 of this report). For the primary and key secondary outcomes the table shows analysis (primary or final or both) each outcome was to be tested, and the order in which they were tested which was set according to a pre-specified hierarchical testing sequence, starting with the primary outcome – the sustained castration rate (Evaluation Criterion 2 (noninferiority) as per European regulatory requirements) and then key secondary outcomes.

At the final analysis testing of two additional key secondary outcomes was planned, conditional to all of the preceding outcomes reaching statistical significance:

- Castration resistant-free survival (CRFS), in patients with metastatic disease and in all patients (i.e. with and without metastatic disease). (numbered 7th and 8th in the sequence of testing, Table 8).
- Time to testosterone recovery back to 280 ng/dL at the 90-day follow-up in patients participating in testosterone recovery follow-up. (9th in the sequence of testing, Table 8).

The CS states that at the final analysis the outcomes previously tested at the primary analysis were to be updated with descriptive statistics (see CS Table 11). However, the final analysis CSR (supplied to the EAG by the company) states that these outcomes were not updated with descriptive statistics. The EAG was unable to identify any data for these outcomes at final analysis.

Table 8 HERO trial hierarchical sequence of outcome testing

Outcomes	Primary analysis	Final analysis
	Fixed testing order for EMA[a]	
Primary outcomes[b]		
Sustained castration rate per Evaluation Criterion 1 (≥ 90% in relugolix)	N/A (FDA only)[c]	Update
Sustained castration rate per Evaluation Criterion 2 (noninferiority)	1 (EMA only)	Update
Key secondary outcomes		
Castration rate on Week 1 Day 4	2	Update
Castration rate on Week 3 Day 1	3	Update
PSA response rate at Week 3 Day 1 (Confirmed)	4	Update
Profound castration rate at Week 3 Day 1	5	Update
FSH level at Week 25 Day 1	6	Update
CRFS during the 48-week treatment in patients with metastatic prostate cancer	N/A	7
CRFS during the 48-week treatment in patients with or without metastatic prostate cancer	N/A	8
Time to testosterone recovery back to 280 ng/dL at the 90-day follow-up in patients participating in testosterone recovery follow-up [d]	9	N/A
Other secondary outcomes		

Outcomes	Primary analysis	Final analysis
Time course and magnitude of sustained profound castration (testosterone < 20 ng/dL)	Not for hierarchical hypothesis testing	
Time to PSA progression		
FSH levels over time		
Timing of testosterone recovery (back to ≥ 50 ng/dL and to ≥ 280 ng/dL or baseline)		
Exploratory efficacy outcomes		
Overall survival	Not for hierarchical hypothesis testing	
Patient-reported outcomes		
EORTC QLQ-C30, EORTC QLQ-PR25, and EuroQoL EQ-5D-5L	Not for hierarchical hypothesis testing	
Safety		
Major Cardiovascular Events	Not for hierarchical hypothesis testing	

Source: reproduced in part from CS Table 11
Abbreviations: CRFS, castration resistant-free survival; EMA, European Medicines Agency; EORTC, European Organisation for Research and Treatment of Cancer; FDA, Food and Drug Administration, FSH, follicle-stimulating hormone; PSA, prostate-specific antigen.
[a] The pre-specified sequential order for statistical testing of outcomes, based on the requirements of the European Medicines Agency.
[b] This outcome is a clinical effectiveness parameter in the economic model
[c] The primary outcome was analysed separately according to the respective requirements of the U.S. FDA and the EMA in Europe.
[d] Originally intended for testing at the final analysis however, at the primary analysis it was analysed for exploratory purposes without formal testing.

EAG comment on study statistical methods

The statistical analysis approach used in the HERO trial is appropriate in design and application. The methods and assumptions used reflect standard practice in phase III clinical trials**.**

3.2.4 Outcomes assessment

3.2.4.1 Efficacy outcomes

The CS describes the clinical effectiveness outcome measures included in the relugolix trials in sections B.2.3, B.2.4 and B.2.6. A range of clinical efficacy outcome measures are included, reflecting the goals of relugolix therapy. These can be broadly summarised as to achieve and maintain serum testosterone suppression to castration levels; changes in PSA levels over time indicative of a treatment response, and recovery of testosterone after cessation of ADT treatment. Table 9 provides a summary of the primary and some of the key secondary outcomes in the HERO trial.

Table 9 Key outcome measures in the HERO trial

Outcome type	Outcome measure	Outcome definition
Primary	Sustained castration rate ≥ 90% for relugolix	Cumulative probability of sustained testosterone suppression to <50 ng/dL from Week 5 Day 1 through Week 49 Day 1 Evaluation criterion 1 (FDA): to determine whether the sustained castration rate is ≥ 90%. Evaluation criterion 2 (EMA): To establish the noninferiority of relugolix compared with leuprolide as assessed by the cumulative probability of sustained testosterone suppression
Key secondary	Profound castration rate	Defined as the cumulative probability of testosterone suppression to < 20 ng/dL prior to dosing at Week 3 Day
Key secondary	PSA response rate	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) (Scher et al. 2016);
Key secondary	FSH concentrations	FSH concentrations and percent change from baseline in FSH at Week 25 Day 1.
Key secondary	CRFS	Defined by disease progression despite achieving testosterone suppression to castrate levels (< 50 ng/dL)

In discussing the outcome measures included in the HERO trial the EAG's clinical expert said that rapid testosterone suppression is relevant in clinical practice. Also, a reduction in MACE is also highly relevant and meaningful for patients.

3.2.5 Efficacy results of the HERO trial

Below, we summarise results from the HERO trial for the primary outcome and selected key secondary outcomes. For brevity we have focused on outcomes which inform the economic model.

3.2.5.1 Sustained castration rate (< 50 ng/dL)

Table 10 summarises the results for the primary outcome, based on two evaluation criteria defined according to the requirements of medicines regulators (1) the FDA and (2) the EMA.

Table 10 Sustained castration rate – HERO trial primary outcome

Primary Endpoint **Sustained castration rate (< 50 ng/dL) from Day 29 through Day 337**	**Relugolix** **(N=622)**	**Leuprolide** **(N=308)**
Evaluation Criterion 1: Castration rate at Day 337 (95% CI)	96.7% (94.9%, 97.9%)	88.8% (84.6%, 91.8%)
Evaluation Criterion 2: Difference from leuprolide at Day 337 (95% CI) p-value	7.9% (4.1%, 11.8%) <0.0001	
Hazard ratio (95% CI)	0.2621 (0.1489, 0.4613)	

Source: Reproduced from CS Table 13

- As the table shows, 96.7% of patients who received relugolix achieved and maintained sustained testosterone suppression below castrate levels (< 50 ng/dL) from Week 5 Day 1 (Day 29) to Week 49 Day 1 (Day 337) (95% CI: 94.9%, 97.9%). The success criterion was that the lower boundary of the 95% confidence interval in the relugolix group should be 90% or higher. The lower bound of the 95% CI was 94.9% and the criterion was met.
- For the second criterion the lower boundary of the 95% confidence interval for the difference between the relugolix group and the leuprolide group should be above the noninferiority margin of −10 percentage points. The between-group difference of 7.9% (95% CI: 4.1%, 11.8%) demonstrated that this criterion was met. It also demonstrated the statistical superiority of relugolix compared with leuprolide (lower bound of the 95% CI greater than 0, with $p < 0.0001$).

3.2.5.2 Time to Prostate-Specific Antigen (PSA) Progression

CS section B.2.6.1.7.d reports the results of time to prostate specific (PSA) progression. PSA progression was defined as the first increase in PSA of 25% or greater and 2 ng/mL or greater above the nadir with confirmation by a second consecutive PSA measurement at least 3 weeks later. For patients without declining PSA from baseline, a PSA increase of ≥ 25% and ≥ 2 ng/mL from baseline beyond 12 weeks was considered PSA progression.

Figure 3 presents the Kaplan–Meier curves showing the time to PSA progression. These curves show that the time to PSA progression was similar between the relugolix and leuprolide arms. A similar proportion of patients had PSA progression in both the relugolix and leuprolide arms (10.1% for each arm). The rate of progression-free survival at the end of treatment (week 49 day 1) was similar in both arms, with a between-group difference of -0.19% (95% CI: -4.49%, 4.11%). The hazard ratio was 0.9932 (95% CI 0.6459 to 1.5272) (p=0.9863), indicating no difference between relugolix and leuprolide. Similar results were observed in the sensitivity analysis when patients were censored at the time of initiating any medications that could affect or alter PSA level.

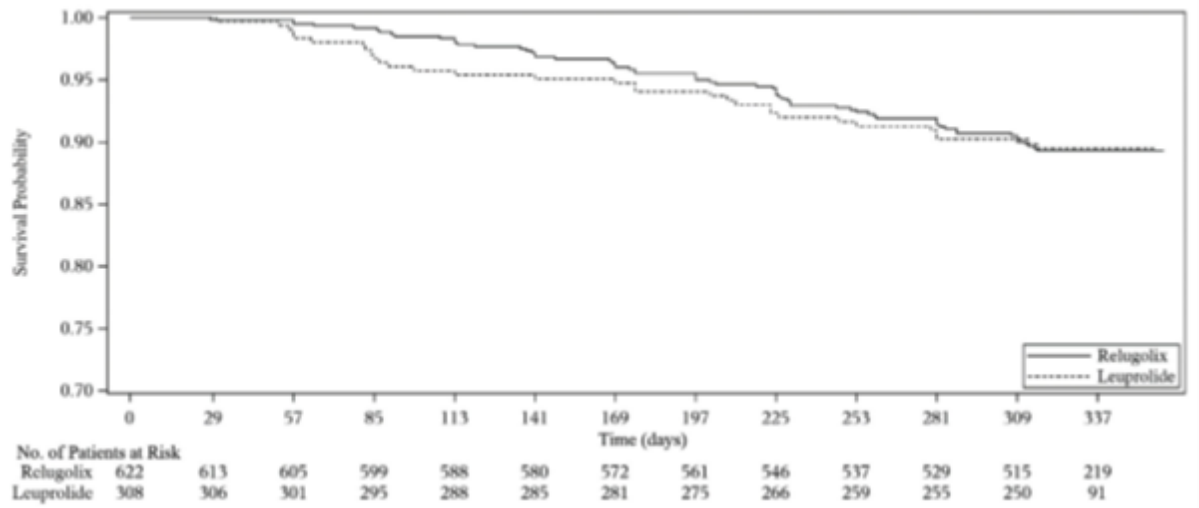


Figure 3 Kaplan-Meier survival curve of time to PSA progression in all patients (modified intention to treat population)

Source: Reproduced from CS document B Figure 13

3.2.5.3 Safety outcomes

Data on adverse events were reported in CS section B.2.10 and CS Appendix F. The majority of patients (>90%) in both the relugolix and leuprolide arms of the HERO trial experienced adverse events. The most common adverse event in both arms was hot flush (Table 11). Serious adverse events were marginally less frequent in the relugolix arm than in the leuprolide arm (12.2% versus 15.3%). The proportion of patients experiencing adverse events with a severity grade ≥3 (i.e. severe, life threatening or death) were similar between the relugolix and leuprolide arms, with the exception of hypertension. Hypertension with a severity grade ≥3 was reported in a greater proportion of patients in the relugolix arm than the leuprolide arm (1.6% versus 0.6%). However, the company state in CS Appendix F that there were no meaningful differences between arms in the mean changes from baseline over time in systolic or diastolic blood pressure or in the proportion of patients with systolic or diastolic blood pressure values meeting the definition of a clinically significant abnormality.

Adverse events led to discontinuations in a greater proportion or patients receiving relugolix compared to those receiving leuprolide (3.5% versus 0.3%). Adverse events leading to treatment interruption only occurred in the relugolix arm (2.7%). The company explain in CS section B.2.10 that the higher incidence of these events in the relugolix arm versus the leuprolide arm is due to the differences in the route of administration between the study drugs i.e. action taken could more often be taken directly for relugolix (daily oral route) versus leuprolide acetate (3-month depot subcutaneous).

A similar proportion of patients in the relugolix and leuprolide arms experienced treatment-related adverse events (73.6% versus 68.8%).

Adverse events that led to a fatal outcome were less frequent in the relugolix arm than in the leuprolide arm (1.1% versus 2.9%). Only one adverse event that led to a fatal outcome was assessed by the investigator as possibly related to study drug. This was an event of acute myocardial infarction in a patient receiving relugolix.

Table 11 reports adverse events reported in at least 10% of patients in either study arm. Constipation and diarrhoea were reported for a higher proportion of patients in the relugolix arm (12.2% each) than in the leuprolide arm (9.7% and 6.8%, respectively). All constipation and diarrhoea adverse events were mild or moderate (grade 1 or grade 2) in severity. There were no serious adverse events of constipation or diarrhoea.

Table 11 Summary of adverse events

Adverse event (AE)	**Relugolix patients N (%)**	**Leuprolide patients N (%)**
Any AE	578 (92.9%)	288 (93.5%)
Serious AE	76 (12.2%)	47 (15.3%)
Grade ≥ 3 AE[a]	112 (18.0%)	63 (20.5%)
AE leading to treatment discontinuation	22 (3.5%)	1 (0.3%)
AE leading to treatment interruption	17 (2.7%)	0
Treatment related AE	458 (73.6%)	212 (68.8%)
Fatal outcome	7 (1.1%)	9 (2.9%)
AE reported in ≥ 10% of patients in either trial arm		
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%)

Adverse event (AE)	Relugolix patients N (%)	Leuprolide patients N (%)
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%)

Source: Partly reproduced from CS document B Table 43 and Table 44.
[a] Adverse event grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03

3.2.5.3.1 Major adverse cardiovascular events

CS section B.2.10.1 and CS Appendix F report results on Major adverse cardiovascular events (MACE) in the HERO trial. The incidence of MACE were identified using a composite query including the Myocardial Infarction Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) (broad), the Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ (broad), as well as deaths due to all causes. These events were not adjudicated and are presented in Table 12 by the presence or absence of self-reported medical history of MACE.

Overall, the proportion of patients in the relugolix arm with reported MACE was approximately half that of the leuprolide arm (2.9% versus 6.2%). Figure 4 presents the Kaplan–Meier curves showing the cumulative incidence of MACE in the relugolix group and the leuprolide group through 48 weeks of treatment. The curves separated within the first four weeks of treatment and remained separate.

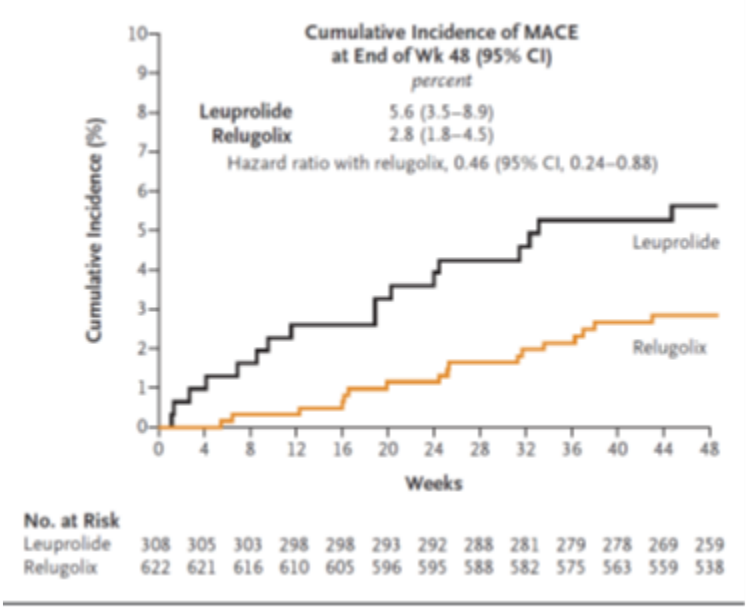


Figure 4 Kaplan–Meier curves showing the cumulative incidence of MACE in the relugolix group and the leuprolide group through 48 weeks of treatment.

Source: Reproduced from Shore et al., 2020. Note that Kaplan Meier curves were presented in CS Figure 20, however the image in the CS was damaged and therefore unsuitable to reproduce here.

The hazard ratio (HR) was 0.46 (95% CI 0.0.2429 to 0.8821) signifying a 54% reduction in the risk of MACE in the relugolix arm compared with the leuprolide arm. The EAG note that this hazard ratio is different from that used in the economic model (HR 0.38; 95% CI 0.18 to 0.79), which has excluded non-cardiovascular deaths, as these deaths are captured separately in the model (CS Appendix O.1.9).

The company performed post-hoc analysis of the incidence of MACE in patients with or without self-reported medical history of MACE (Table 12). For patients with history of MACE the odds of having a MACE after 48 weeks of treatment were 4.8 times greater with leuprolide compared to relugolix (odds ratio (OR) 5.8; 95% CI 1.5 to 23.3). For patients without a medical history of MACE, there was no statistically significant difference as the 95% confidence intervals crossed one (OR 1.5; 95% CI 0.7 to 3.4).

Table 12 Major Adverse Cardiovascular Events with or without a Medical History of a Major Cardiovascular Adverse Event

Adverse event	Relugolix (N = 622)		Leuprolide (N = 308)	
	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
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
Troponin increased	0	1 (0.2%)	0	0
Angina unstable	0	0	0	1 (0.4%)

Adverse event	Relugolix (N = 622)		Leuprolide (N = 308)	
	Patients with MACE MH (N = 84)	Patients without MACE MH (N = 538)	Patients with MACE MH (N = 45)	Patients without MACE MH (N = 263)
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%)
Multiple organ dysfunction syndrome	0	0	1 (2.2%)	0
Transient ischaemic attack	0	0	2 (4.4%)	2 (0.8%)

Source: Reproduced from CS document B Table 45
AE, adverse event; CI, confidence interval; MAC, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; MH, medical history; N, number of patients in the treatment group; n, number of patients with specified AE; 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.

3.2.5.3.2 Adverse events of special interest

Adverse events of special interest in HERO, other than cardiovascular events, were: vasomotor symptoms, carbohydrate and lipid metabolic effects, hepatic transaminase elevations, adverse events related to hypersensitivity, mood disorders, loss of bone mineral density, and QTc prolongation (Table 13). A greater proportion of patients in the relugolix arm experienced hepatic transaminase elevations compared with the leuprolide group (7.6% vs 5.5%). The remaining events of special interest were each experienced in similar proportions in the relugolix versus leuprolide arms.

Table 13 Summary of adverse events of special interest

AE category of special interest	Relugolix N (%)	Leuprolide N (%)
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%)

Source: Reproduced from CS Appendix F Table 91
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; QTc, corrected QT interval
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.

3.2.6 Pairwise meta-analysis of intervention studies

The CS does not report a pairwise meta-analysis of relugolix versus leuprolide (CS section B.2.8) stating “not applicable”. The EAG notes that it is possible to include the HERO trial and the phase II study C27002 in a meta-analysis as they both compared relugolix with leuprolide over 48 weeks and evaluated the effects in terms of sustained castration rates. As we discuss in sections 3.3 and section 3.4 the company included both studies in an NMA (at the request of the EAG).

3.3 Critique of studies included in the network meta-analysis (NMA)

3.3.1 Rationale for NMA

Whilst the HERO trial provides a head-to-head comparison of relugolix versus leuprolide, there are no head-to-head comparisons between relugolix and other comparators listed in the decision problem for the treatment of advanced hormone sensitive prostate cancer. The company therefore performed a network meta-analysis (NMA) to compare treatments through indirect evidence. {Myovant Sciences, 2023 #287;Myovant Sciences, 2022 #286} .The EAG agree that there is a clear rationale for an NMA to be performed.

3.3.2 Identification, selection and feasibility assessment of studies for NMA

The CS reports the results of NMAs relating to two outcome measures: testosterone suppression to castrate levels (CS B.2.9.2.1) and Major Cardiovascular related Events (MACE) (CS B.2.9.2.2). Five studies (HERO, CS21, Heyns 2003, Silva 2012 and Tanaka 2007) were included in the NMA of testosterone suppression.[18 20-23] Company clarification response A11 updated this NMA at the EAG's request to additionally include the phase II study C27002 (NCT02083185).[24] Three studies (HERO, CS21, Margel 2019) were included in the NMA of Major Cardiovascular-related Events (MACE).[18 25 26]

The EAG has identified 3 main issues concerning the identification, selection and feasibility assessment of studies for the NMA.

3.3.2.1 Uncertainty in the number of RCTs considered for potential inclusion in the NMAs

As described earlier (section 3.1), the company conducted an SLR to inform the evidence base for the NMA. There is however, inconsistency within the CS as to how many RCTs were identified by the SLR: CS section B.2.9.1 states the SLR identified 28 RCTs, whereas Appendix D.1.1 states it was 29 RCTs. In response to clarification questions A10 to A14, the company supplied two NMA-related reports, a NMA feasibility assessment report dated 2022 and a NMA report dated 2023. .[27 28] These reports differ as to which SLR searches informed the evidence base, which is shown in Table 14 below:

Table 14 SLR searches included in CS NMA related reports

SLR search date	SLR search included in NMA feasibility assessment report 2022	SLR search included in NMA report 2023
Original search (March 2020)	Yes	Yes
Update search 1 (February 2022)	No	Yes
Update search 2 (April 2023)	No	No

Source: CS Appendix D.1.1., CS NMA feasibility assessment report 2022, [27] CS NMA report 2023[28]

The CS NMA feasibility assessment report conducted in 2022 states that the SLR identified 29 RCTs whereas the CS NMA report conducted in 2023 states it was 28 RCTs.[27 28]

To investigate the discrepancy in the number of studies considered for inclusion in the NMA, the EAG cross-checked information provided in the following sources: Table 1 in the CS NMA feasibility assessment report 2022, which presents studies identified by the original SLR; Table 69 and Table 70 of CS Appendix D.1.1, which provided details of studies included and excluded at the full text screening in the original and updated SLRs; and company clarification response A15. Unfortunately, the CS NMA report 2023 does not report a complete list of the studies identified by the current SLR or included in the NMA report 2023.

The EAG identified one study (EMBARK),[30] which was included in CS NMA feasibility assessment report 2022 but does not appear as an included study in CS Appendix D.1.1. Table 69. The EAG has checked the publication for this study and the study would not meet the inclusion criteria for the current SLR.[30]

Conversely, the EAG identified four studies (NCT00946920, Bolla 2021 (NCT00021450), Tombal 2022 (NCT02972060) and Koontz 2023)[32-35] that appear as included studies in CS Appendix D.1.1 Table 69, but do not appear in CS NMA feasibility assessment report 2022. Company clarification response A15 states that:

- NCT00946920,[32] which compares degarelix to goserelin, was not included in the feasibility report as it did not have a comparable outcome in relation to testosterone suppression. On examining the clinical trial record for this study, the EAG does not necessarily consider this statement to be correct. The primary outcome is the cumulative probability of testosterone at castrate level (≤0.5 ng/mL) defined as the

proportion of patients with testosterone suppression ≤0.5 ng/mL from Day 28 to Day 364.

- The NMA feasibility report (the EAG assume this means CS NMA report 2023) was not updated following the completion of the second update to the SLR, during which studies by Bolla 2021 (NCT00021450), Tombal 2022 (NCT02972060) and Koontz 2023, were identified.[33-35] The company provide reasons why none of the three studies could facilitate an indirect comparison, which the EAG concurs with.
- Of the three studies included in the NMA for MACE, the study of degarelix versus non-specific GnRH agonist treatment by Margel et al (2019)[26] was "*omitted from the search due to an indexing error but would have met eligibility criteria for the NMA*" (CS section B.2.10.2.2). This became apparent after the SLR had completed, though it is not stated how the company became aware of the study. The CS does not describe the indexing error and whether this was an error in the company's search strategy or an error in the indexing of references in the source database searched. Neither is there any mention of whether the error was corrected and the search repeated to identify any other eligible studies which may have been omitted. The upshot of this is that it is uncertain whether other eligible studies could have been included, and what impact these would have on the results of the NMA.

Overall, the EAG considers that the complete list of studies considered for eligibility for the NMA is unclear.

3.3.2.2 Inappropriate NMA exclusion criteria

Compared to CS NMA feasibility assessment report 2022, CS NMA report 2023 and CS Appendix D.1.1 Table 72 report an additional exclusion criterion of Phase II RCTs *"if a Phase III RCT that evaluated the same intervention and comparator(s) was included*". The consequence of this is that study C27002 (NCT02083185) the phase II trial of relugolix was among six studies eligible for the NMA for testosterone suppression in CS NMA feasibility assessment report 2022, but subsequently excluded from the NMA report 2023 and from the NMA presented in CS section B.2.9. The EAG believes the exclusion criteria based on study phase to be inappropriate and requested the company to include this study in the NMAs. In company clarification response A11, the company provides an updated NMA for testosterone suppression that includes study C27002 (NCT02083185) but states it was not feasible to include this study in the NMA of MACE as it did not report MACE outcomes. However, the EAG notes that the clinicaltrials.gov record for this study reports incidence of cardiovascular events within the company's definition of MACE and CV related events.

These data could therefore be used to inform the inclusion of the phase II trial in the NMA for MACE. We discuss this further in section 3.4.4.

3.3.2.3 Uncertainty concerning which outcomes were assessed for feasibility

There is some ambiguity regarding which outcomes were considered for the NMA. In CS section B.2.9.2, it seems to suggest that the following outcomes were considered:

- Cumulative probability of testosterone suppression to <50 ng/dl
- Cumulative probability of profound testosterone suppression to <20 ng/dl
- Mean testosterone levels
- PSA response
- FSH level
- Withdrawals due to adverse events

CS section B.2.9.2 goes on to say that NMAs assessing the efficacy and safety of treatments for HSPC were feasible for two outcomes, testosterone suppression to <50 ng/dl and MACE or CV-related events, without giving evidence why these were feasible but the others were not.

In CS NMA report 2023, CS Document B and CS Appendix D1.1 Table 72 , the outcomes considered for the NMA were slightly different:

- Rates of achieved TS (testosterone <50 ng/dL)
- Rates of prostate-specific antigen (PSA) response (≥50% reduction in PSA)
- Time to PSA progression (PSA ≥25% and ≥2ng/mL above the nadir)
- Overall survival (Kaplan-Meier curves)
- MACE
-

The EAG agree with the CS NMA feasibility assessment report 2022 and CS NMA report 2023 that NMAs are feasible for the following three outcomes:

- Rates of achieved TS (testosterone <50 ng/dL)
- Overall survival
- MACE

However, CS NMA feasibility assessment report 2022, CS NMA report 2023 and company clarification response A15 state that although the NMA for OS was feasible it was not conducted. Reasons given are limited length of follow up and the finding of no differences in

OS between treatment arms in any of the included studies. Overall the company considered the NMA of overall survival "*would be of limited evidentiary value*". Whilst we acknowledge the limitations of the available OS data, if it is feasible to conduct an NMA of OS then the expectation is that this should be done, even if in an exploratory capacity with limitations clearly stated.

EAG comment on identification, selection and feasibility assessment of studies for the NMA

The EAG is unclear whether all relevant studies were identified and considered for eligibility in the NMA. There are two studies that the company assessed as ineligible but which the EAG consider should be in included (NCT00946920 and C27002 (NCT02083185)). It is also unclear which outcomes were assessed for feasibility, although the EAG agree with the feasibility of those reported in the CS NMA feasibility assessment report 2022 and CS NMA report 2023. Of the three outcomes reported as feasible, NMAs were only conducted for two. The EAG believe that a NMA for the third outcome, overall survival, would be informative, even if exploratory in nature.

3.3.3 Clinical heterogeneity assessment

3.3.3.1 Patient population

Company clarification response A14 identifies the following as prognostic factors in hormone sensitive prostate cancer: age, PSA concentration, WHO performance status, Gleason sum score, whether the patient had been diagnosed with synchronous or metachronous metastatic disease, percentage of biopsy-positive core, T-stage, and N-stage. The EAG's clinical expert confirmed that these are the prognostic factors used in clinical practice. Company clarification response A14 also identified two treatment effect modifiers: the proportion of patients with distant metastases and the proportion of patients that have previously received ADT. The EAG's clinical expert did not consider the proportion of patients that have previously received ADT a treatment effect modifier. The expert added that although a proportion of patients in the HERO trial had prior hormone treatment (compared to none in the other studies), clinical rechallenge with GnRH agonists is universally used on relapse. They therefore did not consider the HERO population to be clinically different to the other studies in this regard.

For the five studies included in the testosterone suppression NMA (HERO, CS21, Heyns 2003, Silva 2012 and Tanaka 2007), [18 20-23] the company present study eligibility criteria and a limited selection of baseline characteristics (CS Appendix D Table 74, and CS Appendix D

Table 75, respectively). The EAG asked the company to consider additional characteristics, including any significant prognostic factors (clarification question A13). In their response the company provided baseline data relating to cancer stage and prior treatment for advanced prostate cancer (Table 6 and Table 7 respectively in the company response document). Details of the latter were sparsely reported by the included studies. Moreover, there were no data given on ethnicity and race in the five included studies. The EAG also extracted eligibility and baseline characteristics for two additional studies: Margel et al (2019) [26] for the MACE outcome) and C27002 NCT02083185, the phase II trial comparing relugolix with leuprolide.

The company state that patient age was similar across studies (CS Appendix D.1.1). The EAG also consider patient age to be similar across the studies included in each NMA. Whether the patient had been diagnosed with synchronous or metachronous metastatic disease, and the percentage of biopsy-positive cores were not reported by any of the studies. Data for cancer performance status was only available for one trial included in the NMA for MACE and for four studies in the NMA for testosterone suppression. Among these four studies, two studies each used a different measure of performance status. Gleason score and percentage of patients with metastatic disease were reported in the majority of studies and are presented in Table 15 below (for illustrative purpose the EAG report Gleason score ≥ 8). Gleason score ≥ 8 ranged from 22% to 54%, and the percentage of patients with metastatic disease ranged from 9% to 39%. Baseline PSA levels were not reported in the CS but were extracted by the EAG and are reported in Table 15. Median PSA ranged from 9.4 to 46.8 ng/mL. Overall, the EAG considers prognostic factors, except for age, to be heterogeneous across the studies in each NMA.

Table 15 Baseline characteristics of median PSA level, Gleason score ≥8 and metastatic disease in studies included in the NMAs

Trial name	Treatment	N	Median PSA level (ng/mL)	% with Gleason score ≥8	% with Metastatic Disease
HERO[36]	Relugolix 120mg QD	622	11.7	42.9%	31.8%
	Leuprolide 22.5mg Q12W	308	9.4	43.5%	31.5%
CS21[20]	Degarelix 80 mg Q4W	207	19.8	27%	18%

Trial name	Treatment	N	Median PSA level (ng/mL)	% with Gleason score ≥8	% with Metastatic Disease
	Degarelix 160mg Q4W	202	19.9	28%	20%
	Leuprolide 7.5mg Q4W	201	17.4	26%	23%
Heyns 2003[21]	Triptorelin 3.75mg Q4W	137	46.8	Not reported	38%
	Leuprolide 7.5mg Q4W	140	36.7	Not reported	39%
Silva 2012[22]	Goserelin 3.6mg Q4W	20	Not reported	Not reported	Not reported
	Leuprolide 7.5mg Q4W	20	Not reported	Not reported	Not reported
	Leuprolide 3.75mg Q4W	19	Not reported	Not reported	Not reported
Tanaka 2007[23]	Goserelin 3.6mg Q4W	11	22.0	54%	0%
	Leuprolide 3.75mg Q4W	11	24.0	45%	9%
C27002 (NCT02083185)[24]	Relugolix 80mg	56	≤20ng/mL:75%[a]	25%	11%
	Relugolix 120mg	54	≤20ng/mL:78%[a]	22%	15%
	Leuprolide 22.5mg Q12W	24	≤20ng/mL:88%[a]	29%	13%
Margel 2019 [26]	Degarelix /80mg Q1M	47	11.42	Not reported	27%
	GnRH agonist of clinician's choice Q3M	39	9.5	Not reported	26%

QD, daily; Q1M, once a month; Q3M, once every 3 months; Q4W, once every 4 weeks; Q12W, once every 12 weeks
[a] Percentage of patients with a PSA level ≤20ng/mL

Regarding the NMA for MACE specifically, the EAG note eligibility criteria for two studies (HERO[18] and CS21[37]) excluded patients with ongoing, or history of, specific cardiovascular

events, while another study (Margel et al 2019) [26] required patients to have a documented history of cardiovascular disease. Furthermore, the EAG identified that cardiovascular risk factors, in terms of the proportion of patients at baseline with hypertension or who smoked, were reported for two studies (CS21 and Margel 2019). The proportion of patients with hypertension and the proportion who smoked were respectively 1.4 and 3.6 times greater in Margel 2019 versus CS21. The EAG therefore considers medical history of cardiovascular events and certain cardiovascular risk factors to be heterogenous across studies included in the NMA of MACE.

3.3.3.2 Treatments

Both the NMA for testosterone suppression to castrate levels (CS section B.2.9.2.1) and the NMA for MACE (CS section B.2.9.2.2) require the assumption that leuprolide 7.5 mg every four weeks (Q4W) and 22.5 mg every 12 weeks (Q12W) are equivalent. The EAG clinical expert has confirmed that there are no issues with this assumption.

The study by Margel et al (2019) [26] compares degarelix versus unspecified non-specific (i.e., clinician-preferred regimen) treatment with a GnRH agonist. In order to include Margel (2019) in the network, the company assume the GnRH agonist is leuprolide. The EAG could not find any information in the trial journal publication on which GnRH agonists were prescribed in the comparison group and the proportion of patients taking each. The CS does not state whether the company considered contacting the lead author for clarification on this issue – as would be standard practice in a systematic review. However, the EAG clinical expert confirmed there are no issues with the company's assumption, with clinicians considering GnRH agonists equivalent in terms of CV related adverse events.

The phase II study C27002 (NCT02083185) is a three arm study comparing two doses of relugolix (120mg and relugolix 80mg) to leuprolide. The EAG suspects that the company have pooled data for the two doses in the NMA, even though only one of them is licensed (120mg) (company clarification response A11 Table 1). Similarly, In the NMA for MACE (CS section B Table 35), the company pooled data for both degarelix arms (i.e.degarelix 80mg and degarelix 160mg) of study CS21. The EAG notes that the inclusion of unlicensed doses may impact the relative effect estimates in the NMA, as well as reducing applicability to clinical practice.

3.3.3.3 Outcomes

Regarding the NMA of testosterone suppression, the timing of the castration assessment between studies ranged from 28 days to 364 days (see Table 16 below). The company acknowledge the considerable heterogeneity in timing of castration assessment was a

limitation of the NMA (CS B.2.9.4). The EAG's clinical expert and the EAG agree with the company. The EAG note that the data used by the company for the Heyns 2003 study is for the average 2 to 9 month maintenance of castration. The EAG query why data for this outcome was used in the NMA in preference to the number of patients who had achieved castration at 57 days which was also reported by Heyns 2003.

Table 16 Individual study time points at which testosterone suppression was assessed

Author/Year	Study Name	Threshold	Time Point
Klotz 2008[20]	CS21	50 ng/dL	364 days
CTgov 2018 [24]	C27002 (NCT02083185)	50 ng/dL	25 weeks
Heyns 2003[21]	Heyns 2003	50 ng/dL	2 months
Shore 2020[18]	HERO	50 ng/dL	48 weeks
Silva 2012[22]	Silva 2012	50 ng/dL	3 months
Tanaka 2007[23]	Tanaka 2007	50 ng/dL	28 days

Source: Partly reproduced from CS NMA feasibility assessment report 2022 Table 4

Regarding the NMA of MACE, CS.B.2.9.4 states for the MACE outcome there was heterogeneity with respect to the types of events that were reported but numbers of MIs and fatal CV-related events were available from all three studies.

However, the EAG note that for each of the three studies included in the NMA of MACE there were inconsistencies in the reporting of MACE between the CS NMA feasibility assessment report 2022, CS NMA report 2023, CS Appendix D1.1, CS Appendix D1.1 Table 77, Company clarification response A15 Table 12 and cited sources. For example:

- For the HERO study, CSR protocol Table 8, CSR statistical analysis plan Table 7 and CSR Primary Analysis section 5.2.1.6.6.1 and Table 46 state that MACE were searched for using a composite query inclusive of the Myocardial Infarction SMQ (broad) and Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ (broad), as well as deaths due to all causes. CS NMA feasibility assessment report 2022 section 4.1.5.5 has a similar definition and includes deaths due to all causes. In contrast, a footnote in CS NMA report 2023 section 2.5.2 states that for the purposes of the NMA, only CV related deaths were included in MACE. It is therefore unclear to the EAG, given the difference in MACE definitions, why the same number of MACE (i.e. 18 in the relugolix arm and 19 in the leuprolide arm) are

reported in CSR Primary Analysis Table 46 and CS NMA report 2023 Table 16. The same number of events are also reported in CS Table 35.

- For study CS21, CS NMA report 2023 Table 6 and CS Appendix D.1.1 Table 77 reports myocardial infarction (MI), stroke, ischaemic heart disease (IHD), and fatal CV-related events. However, CS NMA feasibility assessment report 2022 Table 8, and company clarification response A15 Table 12 only report stroke, IHD and fatal CV-related events i.e. MI is not reported as an event. The EAG also note that in CS section B Table 35, the number of MACE events in the leuprolide arm and the pooled degarelix arms (27 and 30 respectively) is less than those reported in the cited source (Smith et al., 2010 Table 6; 28 and 35 events respectively).
- For Margel et al (2019) [26], CS NMA report 2023 Table 6 and CS Appendix D1.1. Table 77 state the types of MACE and CV-related events included in the study were: MI, other non-fatal CV related events and fatal CV related events i.e. stroke and ischaemic heart disease were not reported as events in the study. However, in the cited source (Margel et al 2019), Table 3 reports the number of cerebrovascular accidents in each arm of the study.

Due to these inconsistencies it is unclear which events were considered MACE for each study, which events were included in the NMA of MACE and if the number of events entered into the effect calculations is correct.

EAG comment on heterogeneity assessment

With the exception of age, all other prognostic factors and treatment effect modifiers were heterogenous between the studies included in each NMA. In one trial included in each NMA, the company pooled licensed and unlicensed treatment doses of degarelix There was considerable heterogeneity in the timepoints of the testosterone suppression assessments and there were inconsistences in reporting of specific MACE events.

3.3.4 Risk of bias assessment for studies included in the NMA

The company performed a risk of bias assessment for all studies included in the SLR using the Cochrane Collaboration's Risk of Bias tool 2.0.[38] A summary of the assessments is shown in CS Appendix D.1.3. In response to a request from the EAG, the company also provided an Excel spreadsheet which gave details of the assessments, including judgements for each signalling question of the risk of bias tool for each study. As we discussed earlier in section 3.1, a separate risk of bias assessment should be undertaken for each outcome of interest in each study, to account for study outcomes having different risks of bias in a study

depending on the type of outcome included. However, it appears that the company has reported a single overall risk of bias assessment for each study rather than for individual outcome measures within each study. It is not explicit whether the overall risk of bias assessment per study is based on an assessment of bias in a selected outcome measure or is based on all outcomes (The comments made by the reviewers who applied the criteria included in the Excel spreadsheet indicate it may be the latter). Without this detail it isn't possible to independently cross check the judgements made with the source trial publications. It also means that, potentially, any risk of bias affecting outcomes which were not assessed may be overlooked, giving false confidence in the trustworthiness of the findings.

The EAG therefore carried out its own risk of bias assessments, for the subset of studies included in the original and updated (company clarification response A11) NMA for testosterone suppression, and for the subset of studies included in the NMA of MACE. For two studies (HERO and C27002/ NCT02083185) the source publications used were the CSRs, protocols and statistical analysis plans – all data on file. A summary of the EAG assessments for the outcome of testosterone suppression is presented in Figure 5 and for the outcome of MACE in Figure 6.

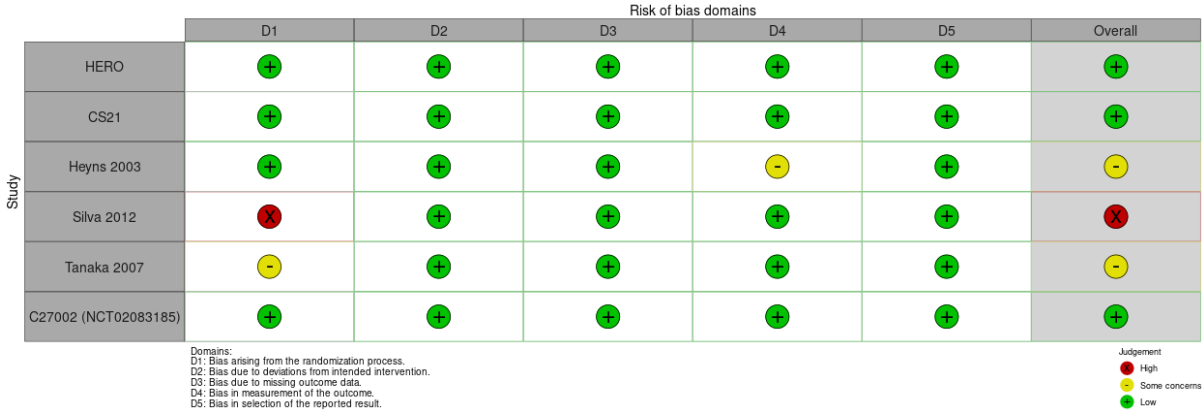


Figure 5 EAG risk of bias assessment for the outcome of testosterone suppression in studies included in the original and updated NMAs of testosterone suppression

Source: Figure created by the EAG using robvis[39]

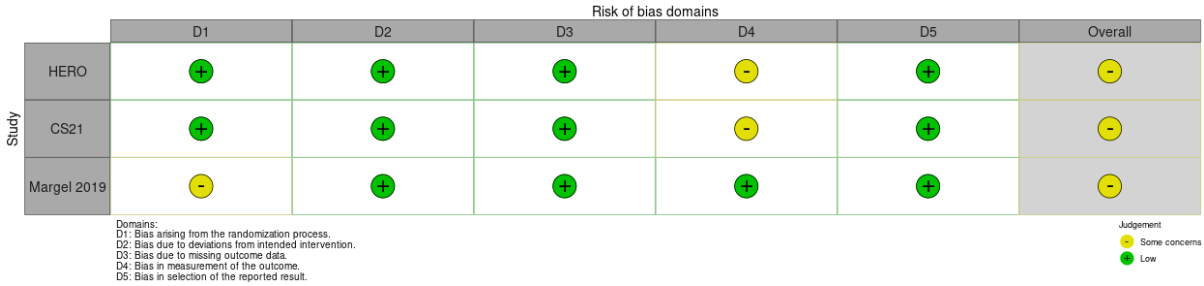


Figure 6 EAG risk of bias assessment for the outcome of MACE in studies included in the NMA of MACE

Source: Figure created by the EAG using robvis[39]

The EAG note that five studies (four of the six included in the NMA of testosterone suppression and all three included in the NMA of MACE), were open label. The EAG believe this is unlikely to bias estimates of testosterone suppression, which we consider a more objective outcome (see D4 in Figure 5). Regarding MACE, the study by Margel 2019 used medical personnel blinded to study outcomes to treat all cardiovascular events and MACE were adjudicated by an expert cardiologist who was blinded to treatment allocation.[26] In HERO, CSR section 5.2.1.6.6 reported that events were not adjudicated.[36] For CS21, it was not reported whether or not events were adjudicated.[25] (see D4 in Figure 6).

For the outcome of testosterone suppression (n=6 studies), the EAG consider three studies to have an overall assessment of low risk of bias (i.e. the risk of bias was low in each of the five domains) (HERO; CS21; C27002) and two studies to have some concerns (i.e. some concerns of risk of bias in one or more of the five domains)(Heyns (2003); Tanaka, (2007)). Only one study was judged at high risk of bias (Silva et al 2012).[22] The cited source publication states that “sixty randomised patients” were “divided into 3 groups of 20, based on a chronological order of arrival". This is not a valid method of randomisation and we therefore consider the allocation method is high risk of bias. A high risk of bias judgement on one or more domains means the overall judgment for that outcome measure in that trial is high risk of bias. Potentially, a case could be made for excluding this trial from the NMA, in a sensitivity analysis for example. However, exclusion of Silva et al from this network would disconnect one of the comparators, the GnRH agonist goserelin, from the analysis.

For the outcome of MACE, the EAG considers some concerns of bias in all three studies included in the NMA. In the study by Margel 2019,[26] this relates to insufficient details of the randomisation process. For HERO and CS21 this relates to the open label design of the study and lack of adjudication of events.

EAG comment on risk of bias assessment in the NMA

The results of the EAG's independent risk of bias assessment for testosterone suppression (the primary outcome in the HERO trial) and for MACE (the composite outcome of cardiovascular adverse events informing the economic model) can be described as mixed. The overall risk of bias for the testosterone suppression result varies from low risk (three studies), to some concerns (two studies) to high risk of bias (one study). The high risk of bias trial (Silva et al) is a pseudo-randomised study and potentially could be removed from the network. However, this trial enables an indirect comparison of relugolix to goserelin, which would be lost. This reduces the certainty of the results of the NMA for this outcome.

3.4 Critique of the NMA methodology

3.4.1 Statistical methods for the NMA

The company used a Bayesian approach to NMA, citing the methodology described in NICE Decision Support Unit (DSU) Technical Support Documents (TSD) number 2 (generalised linear modelling framework) [40] and number 3 (heterogeneity, subgroups, meta-regression and bias). Two modelling frameworks were used: an individual treatment effects model and (ii) hierarchical modelling.

The individual treatment effects framework is widely used in evidence synthesis and in NMA. Each intervention included in the NMA is associated with its own effect estimate relative to another individual intervention. Whilst this is a standard approach to NMA modelling it can be associated with uncertainty when networks include a large number of interventions sparsely populated by a small number of trials. For this reason, Owen et al (2015) developed an approach using a three-level hierarchical NMA model that accounts for exchangeability between treatments within the same intervention class (assuming treatment effects are normally distributed around a class-specific mean and variance) as well as the residual between-study heterogeneity. Owen et al (2015) state that the advantage of this approach is that it enables "strength" to be borrowed within the classes of interventions, strengthening inferences and potentially reducing uncertainty around the individual intervention effects, which increases the ability to rank the interventions and inform decision-making. The CS cites this as the rationale for implementing the hierarchical framework in their NMA. Two intervention classes were defined: GnRH antagonists (relugolix, degarelix) and GnRH agonists (leuprolide, triptorelin, goserelin).

The EAG considers the hierarchical modelling framework can be a useful alternative to the individual treatment effects approach in certain situations. However, it is of questionable

value in the current NMA – for instance, although the network is sparsely populated with a small number of trials the number of interventions (classes) is not extensive (GnRH antagonists and GnRH agonists). The CS does not elaborate on the added value of the hierarchical approach, over and above the individual treatment effects model. There is no commentary on how, or if, "strength" has been gained and uncertainty reduced. And there is no comparison of results with alternative model frameworks. This doesn't necessarily suggest that the results of the hierarchical NMA models in the CS lack validity, but there is a lack of transparency in the rationale for, and application and interpretation of, the hierarchical approach in the current evidence synthesis.

3.4.2 NMA model fitting

For each framework (hierarchical and individual treatment effects) the CS reports the NMA model selection criteria, including: choice of priors (e.g. vague, informative) and goodness of fit statistics. These criteria were considered separately for the two outcome measures included in the NMA (testosterone suppression to castrate levels (<50ng/dL) and MACE or CV-related events), and for the primary NMA analyses and the sensitivity analyses. Table 17 summarises the company's selected NMA models.

- The hierarchical random effects model with informed priors was selected as the best fitting model (based on the lowest DIC value) for the primary analysis of testosterone suppression.
- For the sensitivity analysis of testosterone suppression in which degarelix was excluded from the network (NB. NICE recommends degarelix as an option only for people with advanced HSPC and spinal metastases (TA404). The degarelix trial included in the NMA (CS21) included people at all stages of disease, only 20% were metastatic at baseline) the best-fitting model was the hierarchical random effects model with vague priors. However, the company preferred the same model as used in the primary analysis (i.e. with informed priors). They are not explicit in their reason for not choosing the lowest DIC model but the EAG assumes it is to maintain methodological consistency with the primary analysis.
- For the NMA of MACE or CV-related events the hierarchical models did not perform as well the individual treatment effects in terms of DIC values. Thus for the primary analysis and the sensitivity analysis excluding the study by Margel et al (2019) [26] the individual treatment effects models were selected. (NB. A sensitivity analysis from which Margel et al (2019) was removed was done because the control arm was non-specific GnRH agonist treatment (based on clinicians' discretion) which the company assumed to be leuprolide in the primary analysis. Their concern was that *"This may*

have biased the results to the extent that effects of different GnRH agonists on MACE and/or CV-related events may vary" (CS. section B.2.10.2.2.b)).

- For the primary analysis of MACE or CV-related events the best-fitting model was the random effects individual treatment with vague priors. However, the company chose the random effects individual treatment with informed priors, stating that this model is associated with less uncertainty and may produce narrower credible intervals.
- The company did not report the results of model fitting for the sensitivity analysis excluding the Margel et al. [26] We know that it is a random effects individual treatment model but the prior is not reported in the CS.

The model fitting process appears to have been done assuming that all treatment effects are distributed randomly – there are no details of model fitting assuming the existence of a fixed-effect. The CS states a preference for random effects given the notable between-heterogentiy seen in the studies included in the NMA. The EAG agrees that random effects can be appropriate when there is heterogeneity as it provides a more conservative estimate of relative effectiveness (with wider credible intervals). However, we would have expected the results of model fitting for a fixed-effect analysis to be provided, for comparison with the random effects, but also in the interests of transparency.

Table 17 NMA model fitting results

Details of selected NMA model	**Testosterone suppression**		**MACE**	
	Primary analysis	Sensitivity analysis	Primary analysis	Sensitivity analysis
Framework	Hierarchical	Hierarchical	Individual	Individual
Effects	Random	Random	Random	Random
Company's preferred prior	Informed	Informed	Informed	Informed
Best-fitting prior	Informed	Vague	Vague	NR
Goodness of fit statistic	DIC=53.4 (best-fitting)	DIC=45.4 (company's preference); DIC=45.1 (best-fitting)	DIC=39.6 (company's preference); DIC=38.1 (best-fitting)	NR
Location of NMA results	CS Tables 27, 28	CS Tables 29, 30	CS Tables 36, 37	CS Tables 38, 39

DIC = Deviance information criterion; NR = Not reported

Finally, the CS mentions that model selection criteria also included consideration of “clinical plausibility”, however this isn’t defined in any detail in the CS and the EAG could find no obvious mention of clinical plausibility in the selection of NMA models.

3.4.3 Updated NMA including study C27002

In clarification question A11, the EAG asked the company to include the phase II RCT of relugolix versus leuprolide (C27002, NCT02083185) in the NMA, as we consider that phase II trials should not have been excluded (NB. the company only recently added this exclusion criterion to the NMA). The company responded with an updated NMA on testosterone suppression which included the C27002 trial. The best-fitting model for both the primary analysis and sensitivity analysis excluding degaralix was the random effects hierarchical model with informed priors (i.e. the same as used in the NMA in the CS). However, they did not provide any model fitting results giving details of DIC values, or WinBUGS code used in this update.

The EAG notes that the company may have pooled the two relugolix dosing regimens in study C27002 (relugolix 80 mg (n=56 participants) or 120 mg (n=56 participants)), only one of which is the licensed dose (120mg). This has implications for the effect estimates and their comparability to the NMA in the CS, in which only the licensed dose was used. It also has potential implications for NICE guidance on relugolix which must be based on evidence of its use within the marketing authorisation.

3.4.4 MACE and CV related events in study C27002

The company did not provide an updated NMA for MACE, stating that study C27002 “did not report MACE outcomes” (response to clarification question A11). The EAG considers this to be a factual inaccuracy as the clinicaltrials.gov record for this study (NCT02083185, last accessed 20th March 2024) reports incidence of cardiovascular events within the company’s definition of MACE and CV related events (CS Table 77). These include non-fatal myocardial infarction, non-fatal stroke, and other non fatal CV events (e.g. cerebral haemorrhage, cerebrovascular accident, cardiac arrest, acute coronary syndrome). Some of these measures had low or zero events but nonetheless this isn’t reported in the CS or the company’s response to clarification question A11. The EAG considers the NMA of MACE to be incomplete due to omission of this study.

It is noteworthy that a published meta-analysis of adverse cardiovascular events in GnRH antagonists compared to GnRH agonists by Cirne et al. (2022)[41] (which is discussed in the CS) included both the HERO trial and the phase II study C27002 (NCT02083185). These were pooled with the results of 8 other GnRH antagonist trials (all of which included

degarelix). The pooled risk ratio (95% CI) for GnRH antagonists compared to GnRH agonists was 0.57 (0.39 to 0.81) with no significant heterogeneity (I-squared = 0%; p=0.430). The number of GnRH antagonist-receiving patients was 2415, compared to 1345 GnRH agonist recipients. The EAG notes that the direction of effects for cardiovascular events differed considerably between the HERO trial and the phase II C27002 trial. The risk ratios (95% CI) used in the Cirne et al analysis were 0.47 (0.25 to 0.88) and 1.53 (0.20 to 11.84) respectively. The EAG notes that the absence of statistical heterogeneity adds confidence to the results seen but the wide confidence interval indicates substantial uncertainty which may be due to the relatively small sample size of the C27002 trial (n=136 patients). The marked difference between the relugolix effect estimates is not discussed in the Cirne et al publication, nor in the CS. Moreover, the CS doesn't acknowledge the inclusion of study C27002 in the Cirne et al meta-analysis.[41]

See section 4.2.6.2.4 below for discussion of the implications of uncertainty over the effects of relugolix on MACE incidence for the results of the economic model.

3.4.5 Treatment ranking

In the CS the results of the NMAs are presented in league tables showing relative effect estimates for the various treatment comparisons in each network. The CS also presents the results in a relative ranking of treatments using a method called surface under the cumulative ranking (SUCRA). Using a score from 0-100%, the SUCRA indicates the percentage of treatments in which the treatment of interest has a better outcome. The CS reports a SUCRA ranking for each NMA outcome analysis, in which the treatments are ordered based on probability of having the best efficacy (CS Tables 33, 34, 41 and 42). In each outcome analysis relugolix was ranked 1st suggesting a greater probability of being ranked first compared to other treatments. The EAG notes that ranking methods such as SUCRA are commonly used in published NMAs, but also that they can often be misinterpreted and should not be viewed in isolation from directly observed effects produced by the NMA. As will be seen in the next section, relugolix is not significantly more beneficial than some of the other ADTs, at least in terms of testosterone suppression to castrate levels. But this finding conflicts with the high SUCRA rankings for relugolix. There are other caveats to make in relation to the results of the NMA, notably limitations in the strength and certainty of the evidence base. For this reason, and for brevity, we have not presented the SUCRA rankings in this report.

3.4.6 Summary of EAG critique of the NMA methodology

The EAG is unclear whether all relevant studies were identified and considered for eligibility in the NMA. There are two studies that the company assessed as ineligible but which the EAG consider should be in included: NCT00946920,[32] which compares degarelix to goserelin; and study C27002 (NCT02083185) which compares relugolix versus leuprolide. The latter was included in the NMA at the request of the EAG, but the company only included it for the outcome testosterone suppression to castrate levels. The EAG considers the NMA of MACE to be incomplete without the inclusion of this study.

The CS included the study by Margel *et al* (2019) [26] to the NMA of MACE after the SLR had completed, noting that an indexing error prevented it from being identified by the review. The company do not report whether this error could have affected other eligible studies. It is therefore uncertain whether other eligible studies could have been included, and what impact these would have on the results of the NMA.

There is heterogeneity across the studies included in the NMA particularly in terms of prognostic factors. Medical history of cardiovascular events and certain cardiovascular risk factors to be heterogenous across studies included in the NMA of MACE. The EAG (and expert clinical advisor) and the company agree that there is considerable heterogeneity in timing of castration assessments across studies in the NMA, and that this is a limitation in the certainty of the results.

The EAG notes some inconsistencies within the CS documents and between the CS and source publications in terms of the definition and incidence of MACE events. It is therefore unclear which specific events were included in the NMA of MACE and if the number of events entered into the effect calculations is correct.

The overall risk of bias for the testosterone suppression NMA varies from low risk (three studies), to some concerns (two studies) to high risk of bias (one study). The overall risk of bias for the MACE outcome suggests some concerns in all studies.

The company used a standard Bayesian approach to NMA and this appears to have been implemented appropriately. They adapt this approach by using a hierarchical NMA model, which is an alternative framework for NMA that accounts for exchangeability between treatments within the same intervention class. However, the CS does not adequately justify the added value of this over the standard individual treatment effects approach. There is no comparison of results from the hierarchical model with the results of the individual effects approach.

The NMA model fitting process appears to have been done assuming that all treatment effects are distributed randomly – there are no details of model fitting assuming the existence of a fixed-effect. Whilst the EAG agrees with the company that random effects models are appropriate when there is known heterogeneity, for transparency the fixed-effect model results should be provided as well.

3.5 Results from the network meta-analysis (NMA)

3.5.1 Testosterone suppression to castrate levels (<50ng/dL)

CS section B.2.10.2.1 presents the NMA results for testosterone suppression to castrate levels (<50ng/dL). Table 18 below summarises the results of the primary NMA analysis and the sensitivity analysis in which degarelix was removed. These analyses are presented twice based on the (original) NMA reported in the CS and the (revised) NMA including the phase II study C27002 produced in response to clarification question A11. For each analysis the company report both odds ratios and relative risks, though it is not stated why both are needed. For brevity we summarise just the ORs. The company presents league tables in which the effect estimate for every pairwise treatment comparison can be located. For brevity we just report the pairwise results for relugolix versus each respective comparator. Five trials are included in the original network (HERO, CS21, Heyns (2003), Tanaka (2007) and Silva (2012)) and a sixth trial was added to the revised network (study C27002).

Table 18 NMA Odds ratios of testosterone suppression to castrate levels

	Primary (original)[a]	**Primary (revised)[a]**	**Sensitivity analysis (original)[a]**	**Sensitivity analysis (revised)[a]**
Relugolix	**OR (95% CrI)**	**OR (95% CrI)**	**OR (95% CrI)**	**OR (95% CrI)**
Degarelix	1.19 (0.59, 4.94)	1.03 (0.48, 3.59)	N/A	N/A
Triptorelin	2.13 (0.68, 8.94)	1.50 (0.46, 6.04)	1.05 (0.34, 7.06)	1.15 (1.15, 7.21)
Leuprolide 3M	2.89 (1.46, 6.57)	2.04 (0.88, 4.48)	2.69 (1.19, 6.90)	2.00 (2.00, 5.19)
Goserelin	2.81 (1.08, 12.67)	1.88 (0.66, 8.18)	1.68 (0.70, 13.98)	1.67 (1.67, 10.2)
Leuprolide 1M	2.85 (1.12, 13.05)	1.98 (0.71, 8.40)	2.57 (0.87, 16.59)	1.83 (1.83,10.68)

Source*:* Reproduced by the EAG based on CS Tables 28, 29, company response to clarification question A11 Tables 2 and 4.
CrI = credible interval, N/A = Not applicable, OR = odds ratio,
Yellow boxes indicate statistical significance (credible interval >1); clear boxes indicate no statistical significance. Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W.
[a] Random effects hierarchical model with informed priors (company's preferred model)

As Table 18 shows, for the primary analysis presented in the CS (based on data from 5 trials), there were no statistically significant differences between relugolix and degarelix or triptorelin (as confirmed by credible intervals including 1). However, there were statistically significant differences for relugolix versus leuprolide 22.5mg Q12W/7.5mg Q4W, goserelin and leuprolide 3.75mg Q4W. For the revised NMA including study C27002, (based on data from 6 trials) there were no statistically significant differences between relugolix and any of the comparators. In the sensitivity analyses in which degarelix was removed from the network, the only statistically significant difference in testosterone suppression was between relugolix and leuprolide 22.5mg Q12W/7.5mg Q4W.

The company suggests that that inclusion of study C27002 is the reason for lack of statistical significance in the revised NMA. The study *"did not aim to assess formal statistical differences either between the two relugolix doses, or between relugolix and leuprolide".* The EAG's interpretation of this is that because study C27002 did not include a statistical power calculation for between-group differences in the primary outcome, the study wouldn't necessarily be sufficiently powered to detect significant differences between treatments (i.e. a type 2 error). But that should not necessarily be an argument for not including it in meta-analysis.

3.5.2 MACE

CS section B.2.10.2.1 presents the NMA results for the outcome MACE. Table 19 below summarises the results of the primary NMA analysis and the sensitivity analysis in which the study by Margel et al (2019) [26] was removed. The EAG requested the company to revise the NMA to include the phase II study C27002 (clarification question A11). The company responded that study C27002 did not include MACE outcomes. The EAG, however, disagrees (as discussed earlier in section 3.4.4). Three trials are included in this network (CS21, Margel et al 2019, HERO).

Table 19 NMA Odds ratios for MACE

	Primary (original)[a]	Primary (revised)[a]	Sensitivity analysis (original)[a]	Sensitivity analysis (revised)[a]
Relugolix	**OR (95% CrI)**	**OR (95% CrI)**	**OR (95% CrI)**	**OR (95% CrI)**
Degarelix	0.97 (0.19, 2.61)	NR	0.70 (0.26, 3.04)	NR
Leuprolide	0.39 (0.16, 1.23)	NR	0.46 (0.22, 1.17)	NR

Source*:* Reproduced by the EAG based on CS Tables 36 and 38.
CrI = credible interval, NR = Not reported, OR = odds ratio
Leuprolide 3M: leuprolide 22.5mg Q12W/7.5mg Q4W; Leuprolide 1M: leuprolide 3.75mg Q4W.
[a] Random effects individual treatment model with informed priors (company's preferred model)

As Table 19 shows, there were no statistically significant differences in MACE or CV-related events between relugolix versus the other comparators in the primary analysis and in the sensitivity analysis excluding Margel et al (2019).

3.6 Additional work on clinical effectiveness undertaken by the EAG

None at present.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company's systematic review of economic studies is reported in CS Appendix G. The systematic search was limited to the period from 1 January 2016 to 15 April 2023. The company state that additional relevant articles were 'hand-picked', and that an 'ad hoc' search identified an additional 7 records, but no further information is provided on how this additional searching was conducted.

The PRISMA flow chart (Appendix G Figure 33) reports that 5 full economic analyses (3 cost-effectiveness and 2 cost-utility analyses) were included, of which one UK-based study was considered relevant (Uttley et al. 2017) [42]. The company do not report references for the excluded studies, or for included studies other than Uttley et al. There is also no description of the characteristics of the included studies, including Uttley et al. CS Appendix G refers to Table 47 as a source for this information, but this is not provided in the report.

The paper by Uttley et al. is a summary of the NICE appraisal of degarelix (TA404) [7] authored by members of the Evidence Review Group for that appraisal. The company do not provide a summary of methods or results reported in this paper, although they compare key aspects of the TA404 degarelix model and appraisal in relation to the current assessment in CS Table 49.

> **EAG conclusion**: There are limitations in the company's search for cost-effectiveness evidence and in the reporting of results. We consider whether the company's model and assumptions are consistent with the TA404 analysis and committee conclusions below.

4.2 Summary and critique of the company's submitted economic evaluation

4.2.1 NICE reference case checklist

The EAG assessment of the company's economic analysis in relation to the NICE reference case is shown in Table 20. The reference case criteria are met, with the exception that synthesised evidence is not used for all health effects that drive the economic model. Pooled results from the NMA are used to estimate relative treatment effects on the incidence of MACE for the spinal metastases subgroup, but not for the base case population. And for effects on testosterone suppression, direct effects from the HERO trial are used, with an assumption of equivalence between leuprolide and other GnRH agonists. We discuss this issue in section 4.2.6.1 and Table 20 below.

Table 20 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes (patient only). Carer outcomes are not included
Perspective on costs	NHS and PSS	Yes. NHS costs, and PSS costs for end of life care
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes. Pairwise results reported in response to clarification question B3
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, effectively lifetime (26 years from initial age of 71 in base case)
Synthesis of evidence on health effects	Based on systematic review	Partially. NMA results are not used in the base case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes (EQ-5D used)
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes (from HERO trial)
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes. Utilities mapped from EQ-5D-5L to UK 3L values using the Hernandez-Alava algorithm (CS Appendix P)
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes. No equity weighting or decision modifiers are applied

Element of health technology assessment	Reference case	EAG comment on company's submission
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes (CS B.3.2.2)

Source: Table produced by EAG

4.2.2 Model structure

4.2.2.1 Description of the model structure

The company's model structure is described in CS section B.3.2.2. They developed a health-state transition (Markov-type) model to reflect pathways of disease and treatment progression for a cohort of patients with advanced HSPC. The model uses a three-month cycle length and a lifetime horizon (section 4.2.5 below). The structure is illustrated in CS Figure 21 (reproduced in Figure 7 below).

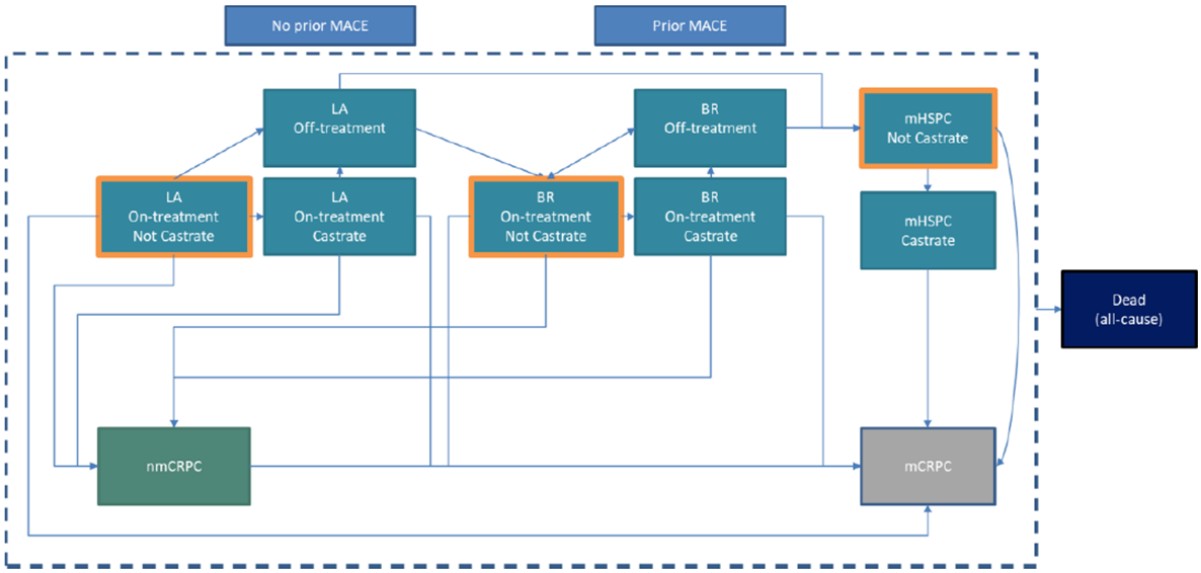


Figure 7 Illustration of economic model structure

Source: Reproduced from CS Figure 21
Abbreviations: LA, locally advanced; BR, biochemical relapse; m, metastatic; nm, non-metastatic; HSPC, hormone-sensitive prostate cancer; CRPC, castration-resistant prostate cancer; MACE, major cardiovascular events. The states outlined in orange are the states that patients can start in.

4.2.2.1.1 Health states

The model includes 10 live health states replicated for patients with and without prior MACE, and two death states (MACE-related and other): 22 health states in total.

The modelled population comprises three subgroups (section 4.2.3):

- Locally advanced (LA) HSPC patients who are not candidates for curative therapy;
- Biochemical relapse (BR) HSPC after local therapy with curative intent, and without metastatic disease; and
- Metastatic hormone sensitive prostate cancer (mHSPC), including patients with BR and evidence of metastatic, as well as those newly diagnosed with metastatic disease.

Patients from these subgroups enter the model at the start of ADT treatment with relugolix or a comparator ('On-treatment'), with serum testosterone above the castrate level of < 50 ng/dL ('Not castrate'). These three initial states (outlined in orange in Figure 7) are replicated for patients with and without a prior cardiovascular event in the 'Prior MACE' and 'No prior MACE' sub-sections of the model. The cohort is thus split between six initial health states, using defined percentages which can be changed for scenario and subgroup analysis. See section 4.2.3 below for further discussion on the model population.

4.2.2.1.2 Health state transitions

Feasible transitions between the health states are illustrated with arrows in Figure 7. The model is programmed using a series of tunnel states, one for each of the 22 health states. Each tunnel state retains information about the time spent in a given health state and tracks all feasible transitions from that state to other health states. The transitions are governed by treatment effects and pathways and natural disease processes, described in CS section B.3.3 and CS Appendix O. We describe these processes below and provide further detail and critique in subsequent sections of this chapter.

Testosterone suppression (section 4.2.6.1)

- If the medical ADT treatment induces a sustained reduction in testosterone to a castrate level (< 50 ng/dL), patients transition from their initial 'Not Castrate' health state to the respective 'Castrate' version of that state. This transition is assumed to occur at the end of the first model cycle (3 months from baseline).
- Patients who do not attain a castrate level of testosterone in the first 3 months remain on treatment in their initial health state until ADT discontinuation, PSA or metastatic disease progression, onset of cardiovascular disease or death.

- In the base case, the probabilities of PSA progression, metastatic progression and overall survival do not differ between 'Castrate' and 'Not Castrate' health states. In addition, utilities are not assumed to differ by castrate status.

Incidence of cardiovascular disease (section 4.2.6.2)

- All patients are at risk of MACE, including non-fatal myocardial infarction (MI), stroke or transient ischaemic attack (TIA), and fatal cardiovascular events. MACE risks differ by ADT type, prior history of MACE and age. Increased risks of MACE with GnRH agonists are assumed to continue for a fixed carryover period after treatment discontinuation.

Treatment discontinuation (section 4.2.8.3)

- A proportion of patients in the LA and BR On-treatment states discontinue the ADT at each model cycle and transition to the respective Off-treatment state. Rates of treatment discontinuation do not differ by ADT drug or by castration status.
- The probability of PSA progression is assumed to increase after discontinuation of ADT, in the Off-treatment health states.
- In the base case, patients with castration-resistant and metastatic disease (nmCRPC, mHSPC and mCRPC) are assumed to continue ADT indefinitely. See also section 4.2.8.4 for discussion of additional subsequent treatment options for people with castration-resistant and metastatic disease.

PSA progression (sections 4.2.6.3.1 and 4.2.6.3.2)

- The probability of PSA progression does not differ by ADT drug, or between people with or without sustained testosterone suppression to castrate levels. People with LA and BR HSPC who are on ADT and experience PSA progression are assumed to become castration resistant, and transition to the nmCRPC state.
- People with LA and BR HSPC who experience PSA progression after discontinuation of ADT are assumed to remain hormone-sensitive and recommence ADT, moving to the BR On-treatment 'Not Castrate' state.
- People with metastatic HSPC, with or without testosterone suppression to a castrate level who experience PSA progression are assumed to be castration resistant, and transition to the mCRPC state.

Metastatic progression (section 4.2.6.4)

- People in all LA and BR states can develop distant metastases and transition to the mHSPC state with a fixed probability per cycle, which does not differ by ADT treatment, or for those with or without testosterone suppression to castrate levels.
- For people with non-metastatic CRPC, the risk of metastatic progression is not affected by type of ADT, but it is reduced with some subsequent treatments (apalutamide, enzalutamide or darolutamide).

Mortality (section 4.2.6.5)

- Patients are at risk of death from fatal MACE and other causes (general population mortality). Patients with metastatic HSPC or CRPC are also at increased risk of death from prostate cancer.

4.2.2.2 EAG critique of model structure and assumptions

The company justify some key features of their economic analysis in relation to conclusions from the NICE appraisal of degarelix for treatment of HSPC in CS Table 49. A list of model assumptions and justification for the company's approach is also provided in CS Table 54. Other model assumptions are discussed in the text in CS sections B.3.2 to B.3.5 and related appendices. We summarise and critique the model structure and key assumptions below.

4.2.2.2.1 Health state transition approach

The company explain that they chose to use a health state transition structure for their model rather than a partitioned survival approach due to the complexity of the disease and treatment pathways, and the short duration of the HERO trial relative to expected times to disease progression and overall survival. The number of PSA progression events observed in the trial was low, particularly for patients with non-metastatic disease (CS Appendix O Figures 38 and 39, and Tables 124 and 125), indicating that parametric extrapolations of PSA progression free survival (PFS) would be highly uncertain. Furthermore, the company note that time to development of metastases was not a planned analysis in HERO, and that data on metastatic progression were not collected (CS Appendix O.1.5).

The EAG agrees that a health state transition approach is appropriate, given the immaturity of progression and survival data. We critique individual sources of evidence used to extrapolate outcomes in section 4.2.6 below, but we agree with the principle of using external sources of evidence to extrapolate long term outcomes rather than relying on immature trial data.

4.2.2.2.2 Face validity of the modelled health states and transitions

The structure of health states and transitions in the company's model generally reflect the processes of disease progression and the treatment pathway.

We have some uncertainties over the way that ADT discontinuation and interruptions are modelled for non-metastatic HSPC. In particular, we question whether it is realistic that discontinuation rates are the same for people with/without testosterone suppression to castrate levels, and whether patients who discontinue ADT would remain off treatment with non-castration levels of testosterone until they experience PSA progression, rather than switching to a different ADT drug. In the base case model, approximately 20% of the initial cohort remain off ADT with non-metastatic HSPC after 10 years.

The model is very complex, with a large number of health states, and multiple tunnel states used to keep track of time on treatment to implement the assumptions on ADT discontinuation and interruption. This creates a practical problem for understanding the model and for validation: we have not been able to conduct usual 'white box' checks of all formulae within the tunnel traces (section 5.5).

4.2.2.2.3 Testosterone suppression has no direct impact on cost-effectiveness

The company explains that although the model captures treatment effects on sustained suppression of testosterone to castrate levels, this does not impact on the cost-effectiveness results (CS B.3.2.2). This results from a series of model assumptions about the lack of effect of castration status on transition probabilities (outlined in section 4.2.2.1.2 above), and the lack of evidence for a direct effect on health-related quality of life (4.2.7.2). These assumptions are generally consistent with committee conclusions in the NICE appraisal of degarelix (TA404) – see CS Table 49.[7] Nevertheless, the conclusion that effective testosterone suppression does not impact on QALYs or the ICER seems counterintuitive, given expert opinion on the clinical importance of rapid testosterone reduction.

4.2.2.2.4 Cost-effectiveness results are driven by treatment effects on MACE

The only advantage of GnRH antagonists over GnRH agonists is therefore their effect on the incidence of cardiovascular events. See section 4.2.6.2 for the EAG critique of model parameters relating to MACE incidence and relative treatment effects. We note some differences in the magnitude of estimated treatment effects on MACE from different evidence sources.

EAG conclusions on model structure and assumptions

- We agree that data from the HERO trial is not sufficiently mature to support a partitioned survival model and agree with the use of a health state transition approach with external data used to inform long-term extrapolations.
- The structure of model health states and transitions generally reflects the processes of disease progression and the treatment pathway, although we have some uncertainties about the modelling of ADT discontinuation, interruption and switching.
- Testosterone suppression does not impact on model estimates of QALYs or ICERs. This appears counterintuitive, considering expert opinion about the clinical importance of rapid testosterone suppression. However, we note that the assumptions underlying this characteristic of the model are conservative, and consistent with conclusions in the NICE appraisal of degarelix (TA404).
- The model includes a large number of health states, with multiple tunnel states used to track time to ADT discontinuation. This makes the model difficult to understand and validate (see section 5.5 for EAG validation methods).
- See Table 45 for a summary of EAG critique model assumptions and additional scenarios and preferred assumptions.

4.2.3 Population

The modelled population is described in CS section B.3.2.1. It comprises three subgroups with advanced hormone-sensitive prostate cancer:

- Locally advanced (LA) HSPC not suitable for curative therapy;
- Biochemical relapse (BR) HSPC following local therapy with curative intent and without metastatic disease; and
- Metastatic HSPC (mHSPC), including patients with BR and evidence of metastatic disease.

The company's analysis does not include patients with high-risk localised disease in the adjuvant or neoadjuvant settings, because the licence extensions for these populations were ongoing during preparation of the submission. The company argues that the model results are likely to be generalisable to people with high-risk localised disease covered by the licence extensions, given that the MHRA granted the extensions without requirement for supplementary data and because the rate of MACE (the key driver for model results) is unlikely to differ for the high-risk localised disease population.

Baseline characteristics for the model cohort are mostly based on the HERO trial population (CS Table 48), including: mean age (71 years); the subgroup distribution (27% LA, 41% BR and 32% mHSPC); body surface area (1.97 m^2); and body weight (81.06 kg).

The company argued that as the HERO trial excluded patients with a history of MACE in the previous 6 months, the proportion of the trial population with prior MACE (37.7%) may not be representative (CS B.3.2.1). They therefore used an alternative source for the proportion with prior MACE in the model cohort: 30.4% from a pooled analysis of six RCTs reported by Albertsen et al. (2014).[43] The company applied an adjustment for age (1.241) to the proportion of prior MACE from Albertsen et al. in the initial submission, but this adjustment was removed in response to clarification question B1, as the mean age in the Albertsen et al. dataset (71 years) was very similar to that in the HERO trial.

The distribution of the cohort between the six starting health states in the base case analysis is shown in Table 21. A clinical expert has advised the EAG that the proportion of patients presenting for treatment with locally advanced disease in clinical practice is likely to be higher than in the HERO trial (particularly given the availability of modern imaging techniques). We report company and base case results separately for the three subgroups to assess whether a different prevalence of the three subgroups would affect cost-effectiveness conclusions.

Table 21 Distribution of base case model cohort between subgroups

Subgroup at baseline	No prior MACE	Prior MACE	Total
LA HSPC	18.8%	8.2%	27.0%
BR HSPC, non-metastatic	28.5%	12.5%	41.0%
Metastatic HSPC	22.3%	9.7%	32.0%
Total in base case analysis	69.6%	30.4%	100.0%

Source: Prepared by EAG from data in CS Table 48 and model
BR biochemical relapse; HSPC, hormone-sensitive prostate cancer; LA, locally advanced; MACE, major adverse cardiovascular event

In addition to the base case analysis, the company report results for a spinal metastases subgroup, for whom degarelix is an additional comparator, as recommended in TA404. Baseline characteristics for the spinal metastases subgroup are assumed to be the same as for the broader metastatic HSPC subgroup.

EAG conclusions on model population

- The company's justification for not using the baseline history of MACE from the HERO trial (37.7%) in their base case model was that this may be an underestimate due to exclusion of patients with a MACE event within six months prior to baseline. However, the rationale for preferring a lower estimate from the Albertsen et al. dataset (30.4%) in this context is not clear. The EAG prefers to use the HERO trial as the source for baseline history of MACE, as this is consistent with other baseline characteristics and clinical outcome data used in the model.
- We question the company's assumption that cost-effectiveness results from the base case model are generalisable to the licence extensions for high-risk localised HSPC in adjuvant and neoadjuvant settings. We raise this as a key issue for further consideration.
- There is some uncertainty over estimates of cost-effectiveness for the subgroup of patients with spinal metastases based on model assumptions and parameters for the broader subgroup of people with metastatic HSPC.

4.2.4 Interventions and comparators

The model includes oral relugolix and three-monthly subcutaneous leuprorelin at licensed doses, as used in the HERO trial (CS B.3.2.3). Two other GnRH agonists, triptorelin and goserelin (both three-monthly subcutaneous injections at licensed doses) are included in the model, as well as degarelix which is recommended by NICE only for use in the subgroup of people with advanced prostate cancer with spinal metastases (TA404).

For their base case analysis, the company use a 'blended comparator' of the three GnRH agonists: 47% leuprorelin, 33% goserelin and 20% triptorelin based on Prescription Cost Analysis data for England (CS B.3.5.1.3).[44] We note that Prescription Cost Analysis data is not specific to the indication and GnRH agonists are prescribed for conditions other than prostate cancer, including endometriosis and pre- and peri-menopausal breast cancer. There is therefore uncertainty over the proportions of different GnRH agonist drugs prescribed for the treatment of advanced hormone-sensitive prostate cancer.

The company assume equal efficacy and safety of the three GnRH agonist drugs, citing the results of their NMA analysis (CS B.2.9), clinical opinion and the committee's conclusions from TA404.[7]

For the base case analysis, the company only report results for relugolix relative to the blended comparator. In response to clarification question B3, the company also report ICERs for relugolix compared with the least and the most expensive GnRH agonists (triptorelin and goserelin respectively). This provides upper and lower limits for the ICER, because the clinical effects, and hence QALYs, are assumed to be equal for all GnRH agonists. The company state that they could not report a fully incremental analysis, because the model structure only has space for two GnRH agonist drugs alongside the blended comparator.

In the spinal metastases subgroup, cost-effectiveness results for relugolix are reported relative to degarelix as well as the blended comparator.

EAG comment on intervention and comparators

- We agree with the assumption of equal efficacy and safety for GnRH agonists used for treatment of hormone-sensitive prostate cancer. This is supported by clinical opinion, available clinical evidence (e.g. as reflected in the company's NMA), and conclusions of the NICE committee for the degarelix appraisal in this patient group (TA404).
- There is some uncertainty over ICERs calculated relative to the blended comparator, because there are price differences between the three included GnRH agonists and uncertainty over their relative use for the treatment of prostate cancer. It is therefore important that incremental cost-effectiveness results are reported for (at least) the most and least expensive GnRH agonists.
- Inclusion of degarelix as well as GnRH agonists is only appropriate for the subgroup of patients with spinal metastases, reflecting NICE guidance (TA404).

4.2.5 Perspective, time horizon and discounting

The model follows the NHS reference case with respect to the perspective for costing (NHS and Personal Social Services), the time horizon (effectively lifetime) and discounting (3.5% for costs and health effects. See section 4.2.1 above.

4.2.6 Treatment effectiveness and extrapolation

In this section we summarise and critique the parameter values used in the company's model to determine treatment effects and rates of disease progression. The company summarise the impact of clinical efficacy outcomes from the HERO trial and NMA in CS section B.3.3. A full list of model parameters is reported in CS Appendix N.

The model includes two measures of treatment effect: testosterone suppression and incidence of major adverse cardiovascular events (MACE). The company note that although there was a significant difference in sustained testosterone suppression between relugolix and leuprolide in the HERO trial, this does not impact on the ICER. This is due to model assumptions that testosterone suppression does not have a direct effect on health-related quality of life or MACE incidence, and the model does not include any other treatment-specific effects on treatment duration, time to PSA progression, time to metastases or non-MACE related mortality. The only clinical benefit of relugolix over the GnRH agonists or degarelix that impacts on the ICER is therefore its estimated effect on MACE incidence. Other aspects of the model only serve to extrapolate overall survival (and hence life years) and the proportion of time spent in health states associated with different health-related quality of life (utilities) and treatment costs.

4.2.6.1 Testosterone suppression

The company's approach to modelling the effects of relugolix and comparators on testosterone suppression is outlined in CS section B.3.3 and Appendix O1.1. We summarise the probabilities of sustained castration used in the company's model in Table 22 below.

For the base case population, the company argue that there is no need to use indirect comparisons, because clinical opinion expressed in the NICE appraisal of degarelix (TA404) was that there is no statistically significant difference in effectiveness between the GnRH agonists. The company therefore use direct estimates of the probability of achieving sustained castration from the HERO trial (testosterone maintained below 50 ng/dL from day 29 to day 337 of the trial) for relugolix (96.7%) and leuprorelin (88.8%),[18] with the same probability as for leuprorelin assumed to apply to goserelin and triptorelin.

For the spinal metastases subgroup, the company states that they used relative risks (RRs) from the testosterone suppression NMA including degarelix (CS Table 28) applied to the probability for leuprolide, with a weighted average of 89.4% for the blended comparator of leuprorelin, goserelin and triptorelin (CS Appendix O Table 123).

The EAG notes that there appear to be errors in the calculation and application of sustained castration probabilities for the spinal metastases subgroup in the company's model:

- The probability for the blended comparator (89.4%) reported in CS Appendix O Table 123 appears incorrect: we replicated this probability using RRs from the fourth column of the NMA matrix (RRs for leuprorelin versus the comparators),

but the correct calculation would use the fourth row (RRs for comparators versus leuprorelin). See the final column of Table 22 for EAG corrected estimates.

- The model applies the same probability (89.4%) for the spinal metastases subgroup for all comparators, including relugolix and degarelix as well as for the blended comparator of GnRH agonists. The reason for using the estimate for the blended comparator for relugolix and degarelix is not explained.

In practice, these discrepancies are not important because, as noted above, the probabilities of sustained castration have no impact on model results (as there is no direct effect of testosterone suppression on utility, treatment duration, incidence of MACE, rates of PSA or metastatic progression, or non-MACE related mortality).

Table 22 Probability of testosterone suppression to castrate levels

Treatment	% GnRH agonists	HERO trial [a] (95% CI)	Base case analysis [b]	Spinal metastases subgroup [c]	Calculated by EAG from NMA [d]
GnRH agonists					
Leuprorelin	47%	88.8% (84.6%, 91.8%)	88.8%	89.4%	*88.8%*
Goserelin	33%	N/A	88.8%	89.4%	*87.0%*
Triptorelin	20%	N/A	88.8%	89.4%	*88.8%*
Blended	100%	N/A	88.8%	89.4%	*88.2%*
GnRH antagonists					
Relugolix	N/A	96.7% (94.9%, 97.9%)	96.7%	89.4%	*94.1%*
Degarelix	N/A	N/A	-	89.4%	*92.4%*

Source: Produced by EAG from CS Tables 13 and 28 and CS Appendix O Table 123.
Abbreviation: N/A, not applicable; NMA, network meta-analysis;
a Proportion of patients achieving castration levels of testosterone (< 50 ng/dL) sustained from day 29 to week 48 in the HERO trial (full analysis set), CS Table 13.
b Probability of castrate in model cycle 1 (3 months from baseline) for the company's base case. Effect for goserelin and triptorelin assumed equal to that for leuprorelin.
c Probability of castrate in model cycle 1 for the company's spinal metastases subgroup. Effect for all drugs assumed equal to weighted mean for blended comparator of GnRH agonists.
d Probability of castrate in model cycle 1 calculated by EAG from the company's NMA RR (CS Table 28) relative to leuprorelin.

EAG conclusion on the estimated effects on testosterone suppression

The company's use of direct estimates of the probabilities of sustained castration from the HERO trial (96.7% for relugolix and 88.8% for leuprorelin) for the base case

analysis, with the assumption equal effects for leuprorelin, goserelin and triptorelin is acceptable. The EAG notes apparent errors in the company's calculation of the probability of sustained castration from the NMA, and in the application of these probabilities in the model for the spinal metastases subgroup. However, these discrepancies do not impact on the cost-effectiveness results, therefore we have not included corrections for these errors in in EAG additional analysis.

4.2.6.2 Major adverse cardiovascular events

The company estimated the probabilities of MACE for relugolix and comparators from a baseline risk of MACE from a US claims database, with adjustment for history of MACE and age; and adjusted for the effects of other treatments using relative risks versus leuprolide (see CS Appendix O1.9).

4.2.6.2.1 Baseline risk of MACE with leuprolide

The baseline risk of MACE with leuprolide was derived from an analysis of a US health insurance claims database (the Marketscan Commercial and Medicare Supplemental Database) reported in an abstract by Brady et al. (2020)[45] (see CS Appendix O.1.9). The study included 41,986 men with prostate cancer, with a mean age of 70.1 years, of whom 8.7% had a MACE prior to initiating ADT and 20.6% had a new MACE while receiving leuprolide during median follow up of 22.8 months. This equates to an annual probability of 11.5% for a mixed population of people with and without a prior MACE.

The company notes several limitations of this analysis. They comment that incidence of MACE in the Brady et al. analysis is likely to be an underestimate, as the MarketScan data do not provide complete ascertainment of medical history. The definition of MACE in the Brady et al. study also differs from that used in the HERO study.

4.2.6.2.2 Adjustments for prior MACE and age

The company used estimates of the relative risk of MACE for patients with versus without a prior MACE (2.62) and the prevalence of prior MACE (13.9%) from the HERO trial, to estimate the annual probability of MACE for people without prior MACE treated with leuprolide:

9.4% = 11.5% /((1-13.9%)+(13.9% * 2.62))

The EAG considers that it would be more appropriate to use the baseline prevalence of prior MACE in the Brady cohort (8.7%) in the above equation to back-calculate the annual

probability of MACE without prior MACE from Brady incidence data. This correction results in a small increase in the estimated probability of MACE for people without prior MACE treated with leuprolide (10.1%), which has a small impact on the ICER.

The baseline probability is adjusted in the model for people with prior MACE, using the relative risk for people with versus without prior MACE from the HERO trial (2.62). The model also includes an adjustment to reflect the increasing risk of MACE with age, based on the hazard ratio from the Framingham Heart Study (3.061).[46]

4.2.6.2.3 Distribution of MACE event types

The distribution of MACE events was based on data from the HERO trial, collated from information reported by Shore et al 2020 and clinical safety data in the HERO Clinical Study Report (See CS Appendix O Table 131). This analysis is based on few events (30 MACE events in total), so there is uncertainty over how representative it is. The relative incidence of MACE events, and in particular the proportion of events that are fatal, is likely to impact on QALYs and hence on the ICER. Table 23 shows the base case distribution using observed events in the HERO trial, and two EAG exploratory scenarios that we used to test the sensitivity of the ICER to changes in the percentage of MACE events that are fatal ([redacted] in the HERO data). See section 6.1 below for results of EAG exploratory scenarios.

Table 23 Distribution of MACE types

MACE type	HERO trial (base case)		EAG scenarios [a]	
	N events	%	15% fatal	40% fatal
Nonfatal MI	[redacted]	[redacted]	31%	22%
Fatal MI	[redacted]	[redacted]	6%	15%
Nonfatal stroke	[redacted]	[redacted]	20%	14%
Fatal stroke	[redacted]	[redacted]	3%	9%
Nonfatal other	[redacted]	[redacted]	34%	24%
Fatal other	[redacted]	[redacted]	6%	16%
TOTAL	[redacted]	[redacted]	100%	100%

Source: Produced by the EAG from CS Appendix O Table 131
MACE, major adverse cardiovascular event; MI myocardial infarction
[a] Illustrative scenarios to assess model sensitivity to the percentage of MACE events that are fatal.

4.2.6.2.4 Treatment effects on MACE incidence

Table 24 summarises MACE probabilities used in the company's base case analysis and estimates with the EAG correction of baseline risk discussed in the section above. For this analysis, the company used a relative risk of MACE calculated from HERO trial data: 0.38

(95% CI: 0.18 to 0.79) (CS Appendix O.1.9, cited as 'data on file'). MACE probabilities for other GnRH agonists were assumed equal to those for leuprorelin, due to a lack of trial evidence for goserelin and triptorelin from the company's systematic review.

For the spinal metastasis subgroup analysis, the company used relative risks from their primary NMA of MACE (CS Table 37). We note uncertainty over these results, indicated by the sensitivity to exclusion of the Margel study[26] (CS Table 37).

Table 24 Annual probabilities of MACE at baseline

Treatment	Company base case		EAG estimates	
	No prior MACE	**Prior MACE**	**No prior MACE**	**Prior MACE**
Leuprorelin	9.4%	24.6%	10.1%	26.4%
Relugolix	3.6%	9.3%	3.8%	10.0%

Source: Produced by EAG from the company's model
Abbreviation: MACE, major adverse cardiovascular event

There is some uncertainty over the relative treatment effects on MACE incidence, as are some differences in estimates from available sources. We summarise estimates from various sources cited in the company submission in Table 25.

Table 25 Relative treatment effects on MACE incidence from alternative sources

Treatment	**Base case CS O.1.9 RR (95% CI)**	HERO trial Shore 2020 [18] HR (95% CI)	**Company NMA** RR (95% CrI)		Cirne et al [41] **MA** RR (95% CI)
			Primary [c]	**Sensitivity** [d]	
GnRH antagonists					
Relugolix	0.38 (0.18-0.79)	0.46 (0.24-0.88)	0.42 (0.19-1.23)	0.84 (0.72, 1.04)	0.57 (0.39-0.81)
Degarelix	N/A	N/A	0.33 (0.15-0.74)	0.82 (0.58, 1.02)	
GnRH agonists					
Leuprorelin	1.00	1.00	1.00	1.00	1.00
Goserelin	1.00 [b]	N/A	N/A	N/A	
Triptorelin	1.00 [b]	N/A	N/A	N/A	

Source: Produced by EAG
Abbreviations: CI, confidence interval; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; MA, meta-analysis; RR, relative risk

[a] Assumed equal to relugolix
[b] Assumed equal to leuprorelin
[c] Primary analysis CS Table 37
[d] Sensitivity analysis excluding Margel (2019),[26] CS Table 39

The hazard ratio reported for the HERO trial by Shore et al. is 0.46 (95% CI: 0.24 to 0.88) (Kaplan-Meier estimates for cumulative incidence, safety population) (CS Table 46).[18] It is not clear why the relative risk used in the company's base case differs from this, although the company note that the definition of MACE in HERO included deaths from all causes, whereas the model captures deaths from non-cardiovascular causes separately from MACE (CS Appendix O.1.9).

The company cited a meta-analysis by Cirne et al. (2022) [41] as supporting evidence for the consistency of the effect of relugolix on MACE incidence. This meta-analysis included 10 RCTs and compared GnRH antagonists (degarelix and relugolix) with GnRH agonists (including leuprorelin and goserelin): relative risk of cardiovascular events 0.57 (95% CI 0.39 to 0.81). We note that the Cirne et al. meta-analysis included data on MACE incidence from the phase II trial of relugolix vs. leuprolide C27002 (NCT02083185), which the company did not include the CS.

4.2.6.2.5 MACE carry-over period

The company discuss observational evidence relating to the effect on cardiovascular risk with GnRH agonists and antagonists, and the effect of intermittent versus continuous ADT (see CS Appendix O.1.9, page 26). They conclude that the risk of MACE for patients treated with GnRH antagonists is similar to that for patients not receiving ADT, but that the MACE risk is elevated while patients are treated with GnRH agonists and that this elevated MACE risk may continue for some time after stopping a GnRH agonist.

These assumptions are coded in the model with a 'carry-over period', during which the raised MACE risk is maintained for some time after discontinuation of a GnRH agonist (i.e. after entry to the LA or BR 'Off-treatment' states). Based on clinical advice, the company estimated the duration of the carry-over period on the mean time to testosterone recovery following discontinuation of GnRH agonist treatment (6.8 months), derived from a study by Nam et al. (2018).[47]

The company test the effect of changing the carry over period in scenario analysis (see Table 37 below).with a shorter (longer) carry-over period QALYs increase (decrease) for the GnRH agonist arm, but there is no change in QALYs for relugolix.

EAG conclusions on estimates of MACE incidence

- There is uncertainty over the company's estimates of the baseline risk of MACE for people with advanced HSPC treated with GnRH agonists. The EAG noted an apparent an error in the adjustment of the baseline risk for people with a history of MACE (section 4.2.6.2.2), but this has a negligible impact on the ICER.
- The distribution of different types of MACE events from the HERO trial is subject to uncertainty, due to the low number of events observed. We explore the impact of uncertainty over the MACE fatality rate (27% in the HERO trial) in EAG analysis.
- The assumption of equal effects on MACE incidence for different GnRH agonists is appropriate, given clinical opinion and the sparsity of evidence for goserelin and triptorelin. We also consider that the assumption of equal MACE effects for different GnRH antagonists (relugolix and degarelix) is reasonable, considering indirect evidence from the company's NMA and the meta-analysis by Cirne et al.
- Estimates of relative MACE effects for GnRH antagonists versus GnRH agonists differ between sources (direct evidence from HERO only, the company's primary and sensitivity NMA analyses, and published meta-analyses (including Cirne et al.). We note that the latter includes data from the phase II trial of relugolix compared with leuprolide (**C27002** NCT02083185), which the company excluded from their submission. The impact of these differences on cost-effectiveness results is explored through company and EAG scenario analysis.
- Evidence for the assumed carry-over period for continuation of increased risks of MACE is weak. We prefer to assume no carry-over in the EAG base case analysis, but to explore the impact of carry-over in scenario analysis.

4.2.6.3 PSA progression

The probabilities of transitions from the hormone sensitive (HSPC) health states to castration resistant (CRPC) health states are determined by estimates of the time to PSA progression. CS Figure 13 shows PSA progression free survival for the HERO trial population. The proportion of patients with no PSA progression over the 48 week trial period was just under 90%, and similar between the treatment arms (CS Table 17). For the model, time to PSA progression was estimated separately for patients with non-metastatic and metastatic HSPC: CS Appendix O sections 1.3 and 1.4 respectively.

4.2.6.3.1 PSA progression for non-metastatic HSPC (LA and BR)

Time to PSA progression for people starting treatment with non-metastatic HSPC was estimated from patient-level data from the HERO trial. Few PSA progression events were

observed over the 48 week trial period (30 events, n=634), and there were no differences between treatment groups, or between locally advanced (LA) or biochemical relapse (BR) subgroups (CS Appendix O Figure 38). The company concluded that long-term extrapolations based on fitted parametric survival distributions would be uncertain, and instead assumed a constant rate of progression (exponential survival distribution) estimated from HERO data for all patients with non-metastatic disease, pooled treatment arms (4.95% per year), see CS Appendix O Table 124).

The company assumed a higher rate of PSA progression for non-metastatic HSPC after ADT discontinuation: a hazard ratio (HR) of 10 was assumed for PSA progression in the LA/BR 'Off-treatment' health states, relative to the corresponding 'On-treatment' health states. This HR was estimated based on clinical advice that the average time for patients to remain untreated would be 2 years. Hence an HR of 10 is required to achieve an annual rate of PSA progression of 50% (10 x 4.95%) while patients are untreated (which is assumed to trigger recommencement of ADT in this patient group).

In the base case, the same rate of PSA progression was applied regardless of ADT type, and for patients with or without sustained testosterone suppression to a castrate level. The company investigated a scenario with an increased risk of PSA progression for people without versus with sustained castration: hazard ratio 1.65 (95%CI 1.19 to 2.30), estimated from Ozyigit et al (2019)[48] and Nabid (2017)[49] (see Table 37),

4.2.6.3.2 PSA progression for metastatic HSPC

More PSA progression events were observed in the HERO 48-week trial period for people with metastatic HSPC (64 events, n=296) than for people with non-metastatic HSPC. The company estimated time to PSA progression for people with metastatic HSPC by fitting parametric survival distributions to HERO data, pooled across treatment arms as no differences in time to PSA progression were observed (CS Appendix O Figures 39 and 40). See CS Appendix R for a description of methods used to fit parametric survival curves.

The company states that hazard rates were 'relatively stable but slightly increasing' over the 48 week period. The EAG questions whether the hazard rate graph in panel B of CS Figure 40 does show an increasing trend.

It is difficult to discriminate between the parametric distributions in terms of statistical or visual fit (CS Appendix O Table 126 and Figure 41). We show summary statistics for selected parametric distributions in Table 26, including the 'best fit' distribution (lognormal), the 'most optimistic' distribution (generalised gamma), and the 'most conservative'

distribution (Weibull). The company assessed the plausibility of the long-term projections from the distributions, referencing rates of PSA progression free survival (PFS) from the placebo arms of the LATITUDE and TITAN trials.[50 51] The company selected the Weibull distribution for their base case, noting that it has a reasonable fit (third lowest BIC), and yields 60-month projections that are closest to the LATITUDE 60-month results. They also conducted a scenario analysis with a lognormal distribution, although this is not reported in the CS.

Table 26 PSA progression in metastatic HSPC: summary for selected distributions

Distribution		AIC	BIC	PSA PFS (months)		
				30	60	120
Best fit	Lognormal	601.7	609.1	47%	27%	11%
Optimistic	Generalised gamma	603.3	614.4	51%	35%	20%
Pessimistic	Weibull (base case)	605.1	612.5	30%	5%	0%
LATITUDE trial (placebo arm)[51]					10%	
TITAN trial (placebo arm)[50]				32%		

Source: Produced by EAG from CS Appendix O.1.4 Table 126 and Figure 42
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PSA PFS, prostate specific antigen progression free survival.

EAG conclusions on PSA progression estimates

- We agree with the use of a fixed rate of PSA progression for people with non-metastatic HSPC. There is uncertainty over the rate estimated from HERO (4.95% per year), due to the low number of events observed.
- There is considerable uncertainty over the relative rates of PSA progression for periods of time when patients are not receiving ADT, compared with periods when they are on ADT (HR=10 assumed for the company base case).
- We agree with the company's approach to extrapolation of PSA free survival in for patients with metastatic HSPC: Weibull survival distribution fitted to HERO data. We also test scenarios with lognormal and generalised gamma distributions, which are associated with lower PSA progression in the long term.
- It is appropriate to use the same PSA progression rates regardless of treatment and castration status. The company tested a scenario with a higher rate of PSA progression for people without testosterone suppression to a castrate level.

4.2.6.4 Metastatic progression

Estimates of metastatic free survival (MFS) are needed to model transitions between non-metastatic and metastatic health states. The company explain their approach to estimating MFS in CS Appendix O1.5. As data on metastatic progression was not collected in the HERO trial, other sources of data were used. The sources differed for hormone-sensitive disease (transitions from LA/BR HSPC to mHSPC); and for castration-resistant disease (transitions from nmCRPC to mCRPC). We discuss these approaches below.

4.2.6.4.1 Metastatic progression for hormone-sensitive prostate cancer (LA and BR)

The company did not identify any trial data from their systematic review that could be used to estimate MFS for hormone-sensitive prostate cancer, so targeted searches were conducted to identify secondary sources. Details of the search methods and findings are not reported.

The model uses a fixed probability of distant metastases, assumed to be constant over time and the same for all treatments. This probability was estimated from an analysis of US SEER cancer registry data linked with Medicare resource use data that provided follow up for 173,462 patients diagnosed with localised prostate cancer between 2000 and 2011.[52] Over this 11-year period, 7.1% of patients developed distant metastases (0.67% per year). The company argue that the SEER/Medicare study is a appropriate source because it is longitudinal analysis from a large nationally representative sample, and it is supported by a similar from a longitudinal study of Japanese patients treated with ADT after radical prostatectomy.[53]

4.2.6.4.2 Metastatic progression for castration-resistant prostate cancer

MFS for nmCRPC was estimated from the placebo arm of the SPARTAN trial of apalutamide.[50 54] This follows the approach in the Institute for Clinical and Economic Review (2018) economic analysis of antiandrogen therapies for non-metastatic prostate cancer.[52] The company digitised the published KM curve and fitted parametric survival distributions. See CS Appendix R for a description of the methods used to fit the parametric distributions, and CS Appendix O for the KM curve (Figure 43), fit statistics (Table 127) and Figure 4 for information on the statistical and visual fit. The fitted MFS estimates were adjusted to reflect the benefit of treatment with Androgen Receptor Inhibitors (ARIs) using hazard ratios in CS Appendix O Table 128.

The company noted that the distribution with the best statistical fit (generalised gamma) did not have a good visual fit to the KM data. They therefore chose the lognormal distribution for the base case analysis because this had the best visual fit and also a good statistical fit (third lowest BIC). We summarise information for selected parametric survival distributions in

Table 27. In addition to the company's base case (lognormal) and the best fitting distribution (generalised gamma), we include the Weibull distribution as an example of a more pessimistic projection.

Table 27 MFS progression for nmCRPC: summary for selected distributions

Distribution		AIC	BIC	MFS adjusted for ARI [a] (months)		
				36	60	120
Best fit	Generalised gamma	1522.2	1534.2	69%	64%	57%
Base case	Lognormal	1546.0	1553.9	59%	45%	28%
Pessimistic	Weibull	1576.4	1584.4	54%	30%	5%

Source: Produced by EAG from CS Appendix O.1.5 Table 127 and the company's economic model
AIC, Akaike Information Criterion; ARI, Androgen receptor inhibitor; BIC, Bayesian Information Criterion; MFS, metastatic free survival.
[a] Adjusted for treatment with Androgen Receptor Inhibitors (ARI), see CS Appendix O Table 128

EAG conclusions on estimates of metastatic progression

- The assumption that the risk of development of distant metastases is constant for people with LA or BR HSPC is reasonable, given the slow rate of metastatic progression in this population. The estimated rate in the company's model (approximately 0.7% per year) is derived from an large dataset with over ten years of follow up, although there may be a question over the generalisability US data from 2000-2011 to the current UK context. We test the sensitivity of cost-effectiveness results to this parameter (see section 6.1).
- The company use appropriate methods to estimate MFS curves to model time to metastatic progression for people with castration-resistant prostate cancer. They do not justify the use of data from the SPARTAN trial, but refer to a good quality economic evaluation that followed a systematic approach to select this source. The decision to use a lognormal survival distribution for the base case analysis is reasonable. We test the impact of alternative distributions (see section 6.1).

4.2.6.5 Mortality

The model estimates mortality based on three sources:

- *Deaths related to cardiovascular disease*: MACE-related mortality is estimated based on the overall incidence of MACE, and the proportion of MACE events that are expected to be fatal, as described in section 4.2.6.2.3 above.

- *Deaths related to prostate cancer*: Mortality rates for people with metastatic prostate cancer were estimated from published sources. For castration-resistant disease (mCRPC), overall survival curves were estimated from the PREVAIL trial.[55] These rates were then adjusted for people with hormone-sensitive prostate cancer (mHSPC) using a hazard ratio for HSPC versus CRPC reported by Hussain et al (2018)[56].
- *Deaths from other causes*: National life tables are used as a lower limit, to ensure that death rates for people with prostate cancer cannot be lower than for men of the same age in the general population (ONS England and Wales 2021).

4.2.6.5.1 Overall survival for metastatic CRPC

The company fitted parametric survival distributions to a published KM curve for overall survival (OS) from the placebo arm of the PREVAIL trial of enzalutamide plus ADT versus ADT alone for mCRPC.[55] This source was identified from the report of the economic analysis conducted for the Institute for Clinical and Economic Review's evaluation of treatments for nmCRPC.[52] The OS KM for the PREVAIL placebo arm relates to expected outcomes with ADT alone. The company therefore adjusted the fitted OS curves to account for additional treatment with ARIs or chemotherapy, as included in the model (see hazard ratios in CS Appendix O Table 130).

CS Appendix O.1.7 shows the reconstructed OS KM curve from the trial (Figure 45), the fitted parametric OS curves (Figure 46) and goodness of fit statistics (Table 129). The company selected the log-logistic distribution for their base case, as this had a good visual fit and a good statistical fit (second lowest BIC). We show summary statistics for the lognormal (best fit) and Weibull (pessimistic) distributions in addition to the log-logistic (base case) distribution in Table 28. Projected survival from other parametric distributions were similar, and had very little impact on the ICER.

Table 28 Overall survival for mCRPC: summary for selected distributions

Distribution		**AIC**	**BIC**	**MFS adjusted for ARI [a] (months)**		
				36	**60**	**120**
Best fit	Lognormal	2907	2916	55%	36%	16%
Base case	Log-logistic	2913	2922	52%	32%	14%
Pessimistic	Weibull	2916	2925	49%	20%	1%

Source: Produced by EAG from CS Appendix O.1.5 Table 127 and the company's economic model
AIC, Akaike Information Criterion; ARI, Androgen receptor inhibitor; BIC, Bayesian Information Criterion; MFS, metastatic free survival.

[a] Adjusted for effects of additional treatment with Androgen Receptor Inhibitors (ARI) or chemotherapy, see CS Appendix O Table 130

4.2.6.5.2 Overall survival for metastatic HSPC

The company did not find data on mortality for people with metastatic HSPC. They therefore estimated survival for this population by adjusting the above OS estimates for metastatic CRPC, using a hazard ratio reported by Hussain et al (2018)[56]: 2.49 (95% CI: 2.13, 2.91) for mCRPC versus mHSPC, or 0.40 (1/2.49) for mHCPC versus mCRPC. Results are not sensitive to changes in this parameter.

4.2.7 Health-related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic review to identify HRQoL utility data for patients with prostate cancer treated in the first-line setting (CS Appendix H). The searches were performed between 1st January 2016 and 15th April 2023, and the inclusion criteria are shown in CS Appendix H Table 103.

Eight studies were identified, and these are summarised in CS Appendix H Table 106. Two studies were conducted in the UK: an observational study by Parry et al. 2020 [57] and a literature review and questionnaire by Hall et al. 2019 [58]. The methods used to derive utilities in six studies were EQ-5D-3L and EQ-5D-5L.

4.2.7.2 Study-based health-related quality of life

HRQoL data were collected from patients in the HERO trial using the EQ-5D-5L questionnaire. The company estimated utility values from these data by mapping to the EQ-5D-3L using the Hernandez-Alava algorithm [59] and Dolan et al. (1996)[60] UK value set, as recommended by NICE.[61] Mean baseline utilities for patients in the HERO trial are shown in CS Appendix P Table 137.

The company used generalised estimating equation (GEE) regression models to estimate utilities for the model health states from the trial data. The methods are described in CS Appendix P.1.1.

Health state utilities per health state are presented in CS Appendix P1.1 Table 141. The company assume that the health state utilities are the same among the ADTs. They also assumed that the health state utilities for the LA, BR, and mHSPC states do not differ for

patients with testosterone below the castrate level versus those above this level. Thus utilities do not differ by castration status.

The EAG noted that covariates related to castration levels of testosterone suppression were not included in the final GEE regression equation used to calculate health state utilities for the model (CS Appendix P Tables 140 and 141). The company stated that the decision to exclude castration status as a covariate was because they considered that the results in the model that included this variable (Model 3 in CS Appendix P Table 139) were counterintuitive, which they ascribed to the small number of observations for patients who had not achieved castration levels of testosterone. In clarification question B7, we asked the company to repeat the regression used in the model (CS Appendix P Table 140) with castration as an additional covariate to assess whether and how this would change the estimated health state utility values. The company did not do this, stating that the castration level was not included in the final GEE regression equation to avoid confounding, due to similar definitions and timing of PSA and castration assessment.

4.2.7.3 Health state utility values used in the economic model

Health state utility values in the economic model were taken from the HERO trial and are presented in CS Appendix P.1.2. Table 142. The EAG observed that the reported mean utility at baseline for participants in the HERO trial used in the economic [redacted]. [redacted] In response to clarification question B9, the company adjusted the health state utilities in the model to be consistent with general population norms for men of the same age. The utility values in the model are age-adjusted using general population utility values, which were initially taken from Kind et al 1999.[62] The company updated the source of general population utilities using the equation reported by Ara and Brazier (2010)[63] as requested by the EAG in clarification question B8.

Disutilities were applied for patients experiencing nonfatal MACE and non-MACE grade 3-4 adverse events. Disutility values were taken mainly from NICE TA404[7] (nonfatal MACE) and NICE TA712[14] (non-MACE adverse events), shown in CS Table 51. Disutilities were applied by multiplying the disutility by the duration of each adverse event, adjusted by the cycle length. In response to clarification question B10, the company updated the economic model to include the injection site reaction disutility shown in CS Table 51.

We summarise the sources used to estimated utility parameters in Table 29 and the base case values in Table 30.

Table 29 Summary of utility parameters used in the economic model

Parameter	Reference in the CS	Source	Comments
Health State utility	CS Appendix P.1.2. Table 142	HERO trial (data on file)	Analysis of prospective EQ-5D data taken from trials. The values were adjusted to align with the general population utility (clarification question 9)
Age and sex-matched general Population Utility	The equation is in the reference source	Ara and Brazier 2010[63]	Updated in the CS after the EAG request (clarification question 8).
Non-fatal MACE disutility	CS Appendix P.1.2. Table 142	NICE TA404[7]	Values assessed in NICE TA404
Non-MACE disutility	CS Table 51	NICE TA712[14] and literature	Values assessed in NICE TA712

Table 30 Summary of utility and disutility values for cost-effectiveness analysis

Health states	Original Utility from HERO trial	Adjusted utility[a]
LA on treatment not castrate	[redacted]	[redacted]
LA on treatment castrate	[redacted]	[redacted]
LA off treatment	[redacted]	[redacted]
BR on treatment not castrate	[redacted]	[redacted]
BR on treatment castrate	[redacted]	[redacted]
BR off treatment	[redacted]	[redacted]
mHSPC not castrate	[redacted]	[redacted]
mHSPC castrate	[redacted]	[redacted]
nmCRPC	[redacted]	[redacted]
mCRPC	[redacted]	[redacted]
MACE disutility		
MACE disutility, nonfatal myocardial infarction	-0.0900	

Health states	Original Utility from HERO trial	Adjusted utility[a]
MACE disutility, nonfatal stroke	-0.0900	
MACE disutility, nonfatal other CV	-0.0900	
Adverse event disutility		
Fatigue	-0.131	
Arthralgia	-0.069	
Hypertension	-0.153	
Injection site reaction	-0.011	

Source: CS Appendix P.1.2.Table 142 and company's economic model
LA: locally advanced, BR: biochemical relapse, mHSPC: metastatic hormone-sensitive prostate cancer, nmCRPC: non-metastatic castration-resistant prostate cancer, mCRPC: metastatic castration-resistant prostate cancer, MACE: Major cardiovascular events
a Adjusted utility in response to the clarification question B9

EAG comment on HRQoL

The company's approach to estimating utility values is reasonable and consistent with the NICE reference case. The utility values for the LA, BR, mHSPC, nmCRPC, and mCRPC were taken from the HERO trial. The EAG requested two adjustments, made by the company: (i) adjust the health state utilities in the model to be consistent with the general population norm for men of the same baseline age (clarification question B9); (ii) update the age adjustment of the utility values using the estimates from Ara and Brazier 2010.[63]

4.2.8 Resources and costs

The economic model includes drug acquisition and administration costs for first and subsequent treatments, follow-up costs, costs for antiandrogen treatments during initial ADT, costs for managing adverse events (MACE and non-MACE events) and end-of-life costs.

The company conducted a literature search in March 2023 to identify costs and resources used for first-line treatment and management of prostate cancer. Details of the search strategy and eligibility criteria are shown in CS Appendix I Tables 107 (EMBASE) and 108 (MEDLINE). A total of three studies met the inclusion criteria; two of these were conducted in the UK.[64 65] The two studies are shown in CS Appendix I Table 110. The EAG observed that the company's literature search was nine months old at the time of the submission.

4.2.8.1 Drug acquisition

Relugolix is administered orally 30 minutes before breakfast. Patients receive a loading dose of 360mg for one day and subsequent maintenance doses of 120mg daily. Relugolix is available in packages of 30 tablets (120mg each) with a list price of £150.16. Relugolix is available with a patient access scheme (PAS) price discount of [redacted]

The blended comparator includes the following GnRH agonist medications:

- Goserelin is administered via subcutaneous injections of 10.8mg dose every three months. A goserelin vial is available with a list price of £235.00
- Leuprorelin is administered via subcutaneous injections of 11.25mg every three months. The company assumed that bicalutamide would be administered orally with leuprorelin for all patients for the first three weeks of treatment to control the testosterone flare. A leuprorelin vial is available with a list price of £225.72, and bicalutamide is available in packages of 28 tablets (50mg each tablet) with a list price of £2.03.
- Triptorelin is administered via intramuscular injections of 11.25 mg every three months. A triptorelin vial is available with a list price of £207.00.

The cost of the blended comparator was calculated as a weighted average of the costs of goserelin, leuprorelin and triptorelin, considering their proportions in the prescription cost analysis[66] (33%, 47%, and 20%, respectively), which is £225.11 every three months.

Degarelix was considered for the subgroup of mHSPC patients with spinal metastases, as recommended by NICE (TA404[7]). Degarelix is administered as subcutaneous injections in a loading dose (240mg) and subsequent doses of 80mg every 28 day cycle and has a list price of £260.00 (package with two 120mg vials) and £128.27 (package with one 80mg vial), respectively.

The dosages and cycle lengths are shown in CS Appendix Q Table 143, and the drug unit costs are in CS Appendix Q Table 144. No vial sharing was assumed for IV therapies. Costs of the comparator ADTs (leuprorelin, goserelin, triptorelin, degarelix) and antiandrogen treatments (bicalutamide) were taken from the British National Formulary (BNF). Costs of the subsequent treatment medications were taken from the BNF (apalutamide, enzalutamide, darolutamide, and abiraterone) and the electronic market information tool (eMIT) (docetaxel, cabazitaxel, prednisolone and dexamethasone). The company used the manufacturer list price for radium-223, as reported in NICE TA412[67] and adjusted by inflation[68].

The EAG notes a disagreement between the price of docetaxel and cabazitaxel presented in CS Appendix K Table 116 (BNF prices) and the company assumption (eMIT prices) in CS Appendix Q Table 144. This was corrected in response to clarification response B13. In addition, the daily dose for radium-223 was amended in the CS from 1.35 μci to 1.49 μci in CS Appendix Q Table 143 in response to the clarification question B14 to match the correct dose of 55kBq/kg body weight (NICE TA412).[67]

In CS 3.5.1.6, the company stated that medication with IV administration would include the cost of whole vials only (no vial sharing). In this case, if the estimated number of vials needed for a dose is a fraction, the number must be rounded up to calculate the drug acquisition cost, and the complement fraction was considered drug wastage. However, this drug wastage was selected for the base case analysis (SubTxCalc sheet).

The EAG has replicated the company's analyses using all applicable PAS prices in a separate confidential appendix to this report.

4.2.8.2 Drug administration

Administration costs are taken from NHS Reference Cost 2021-2022 [68] and NHS Payment Scheme 2023/2025, 2023/2024 price workbook.[69] Oral treatments are assumed to have no administration cost. The company considered that intramuscular depot injections could be carried out in primary or secondary care, in line with NICE TA404.[7] The administration cost does not include the cost of syringes for intramuscular injections. The administration costs per method of administration and proportions are shown in Table 31.

Table 31 Drug administration costs

Drugs	Method admin.	Admin. cost	Proportions in the CS	Proportions in IQVIA
Relugolix, apalutamide, bicalutamide, enzalutamide, darolutamide, abiraterone, prednisolone, dexamethasone	Oral	£0.00	Costs of administering oral medication was assumed to be negligigle.	
Leuprolide, triptorelin, goserelin	Intramuscular depot injection	£25.28	87% primary, 13%	87.58% primary,

Drugs	Method admin.	Admin. cost	Proportions in the CS	Proportions in IQVIA
			secondary care	12.42% secondary care
Degarelix	Intramuscular depot injection	£29.44	80.84% primary, 19.16% secondary care	81.59% primary, 18.41% secondary care
Docetaxel, radium-233, cabazitaxel	Intravenous injection	£286.71		

Source: NHS Payment Scheme 2023/2025, 2023/2024 price workbook [69], IQVIA data[66]

The EAG observed minor discrepancies in the proportions of primary and secondary care services for intramuscular injection administration after evaluating the IQVIA data source{Iqvia, 2023 #125} provided by the company in response to the clarification question B15 (please see Table 28). The EAG also noted minor discrepancies in the proportion used to calculate the administration cost for degarelix, which is not mentioned in CS.3.5.1.5 but is modelled in the economic model.

In response to clarification question B16, the company updated the intravenous administration cost in the CS from £362.00 to £286.71, considering a weighted average from three service codes ("day case and reg day/night", "outpatient", and "others") associated with the HRG code SB12Z ("deliver simple parenteral chemotherapy at first attendance") provided by the national NHS reference costs 2021/2022.52

In NICE TA404 (section 7.5.5, and ERG report section 5.2.8), the proportion of cost administration for degarelix was 50% by a practice nurse in a GP surgery and 50% by a nurse in a hospital.

4.2.8.3 ADT treatment duration

The CS included some statements that patients in LA and BR states who failed to achieve a castration level of testosterone suppression (LA/BR On treatment not Castrate health state) after one model cycle would switch to a different type of ADT (CS B.3.5.1.4 and CS Appendix O.1.3 page 6). These appear to be drafting errors, as the EAG was unable to verify coding of ADT treatment switching within LA/BR HSPC health states. Our understanding is that patients with LA/BR HSPC who do not achieve a castrate level of

testosterone remain in the 'On-treatment, Not castrate' health state, and remain off treatment until PSA or metastatic progression (or death). The probabilities of ADT treatment discontinuation in LA and BR states are presented in CS Appendix O Table 133. The EAG requested the Symphony claims database in clarification question B5 and verified the probabilities in Table 133.

Patients in the mHSPC state are assumed to receive ADT indefinitely. Likewise, the EAG could not verify the company's assumption of switching the type of ADT in the case of one patient who failed to achieve sustained castration level.

The duration of ADT therapy in the nmCRPC and MCRPC states is discussed in section .4.2.8.4 below.

4.2.8.4 Subsequent treatment

The economic model has three options for ADT after PSA progression while on treatment: remain on the initial ADT; switch to an ADT mix; or interrupt ADT.

In the base case, the company assumed that all patients progressing to a CRPC health state (non-metastatic or metastatic) would have the subsequent treatment and remain receiving their initial ADT indefinitely. In a scenario where a patient interrupts their initial ADT, the model has an option to assume use of a different ADT when treatment is recommenced, represented in the model as an ADT mix. The cost of the ADT mix is a simple average of the ADT costs (list prices of leuprorelin, goserelin, and triptorelin). The EAG observed a discrepancy in the ADT mix cost: the company assumed an ADT mix cost of £197.43 per three-month model cycle in CS.3.5.1.4, and the EAG calculated the ADT average cost of £229.39 per three-month model cycle.

The CS assumed that patients with non-metastatic CRPC would continue to receive their initial ADT indefinitely, with the addition of an ARI treatment. The therapies considered for nmCRPC were apalutamide, enzalutamide or darolutamide. CS Appendix O.1.10 Table 134 provided the duration of treatment and the proportion of patients receiving each ARI for nmCRPC. The duration of treatment with each ARI was taken from a trial-reported median duration of therapy. The proportion of patients in each treatment was assumed to be equal. Clinical advice to the EAG informed that enzalutamide is not recommended for non-metastatic CRPC treatment in NHS England and Wales, confirmed in NICE TA580[13]. Therefore, the subsequent treatment for nmCRPC should include only apalutamide and darolutamide.

Patients who progressed to metastatic CRPC were also assumed to continue to receive their initial ADT indefinitely, with added ARI or chemotherapy. The treatments considered for mCRPC were enzalutamide, abiraterone, docetaxel, dexamethasone, radium-223, and cabazitaxel with prednisolone. CS Appendix O.1.10 Table 135 provides the duration of treatment and the proportion of patients receiving each ARI for mCRPC. The duration of each treatment with ARI was taken from a trial-reported median duration of each therapy, and the company assumed that the same proportion of patients would use each one of these therapies. Clinical advice observed that the proportion of subsequent treatment to the mCRPC should have more patients receiving chemotherapy and fewer patients receiving radium-223 and cabazitaxel. Also, the clinical advice observed that abiraterone is not currently approved by NICE in NHS England, but it is used in NHS Wales and Scotland.

The cost for the ARI medications and chemotherapies are in CS Appendix Q Table 144. The one-off cost of subsequent treatment for CRPC health states was estimated by multiplying the per-cycle cost of each treatment (c_{ARI}) by the per-cycle duration of the therapy (d_{ARI}) and the proportion (ω_{ARI}) of the treatment.

The EAG notes one error (duration of treatment) in the nmCRPC subsequent treatment costs. Another error was found in the mCRPC subsequent treatment costs related to the drug wastage of IV therapies. Both errors are in the subsequent treatment calculation worksheet (SubTxCalc). We correct these errors in section 5.5.2.

Table 32 below summarises the subsequent treatment costs for the nmCRPC and mCRPC health states. The proportions are an assumption from the company based on clinical expert opinion. Clinical advice to the EAG was that the proportions for the mCRPC health state could differ, with more patients taking chemotherapy than radium-223 and cabazitaxel. The EAG have evaluated the proportions (and consequently, the one-off costs) of subsequent treatment in two scenarios (see section 6.3): for comparison, we compare scenarios with the least expensive ARI options and the most expensive ARI option for each health state.

Table 32 Subsequent treatment costs with EAG corrections

ARI	Proportion	Duration (cycle)	Cost (£/cycle)	One-off Cost (£)
ADT alone	100%	1	£197.43	
Non-metastatic cancer-resistant prostate cancer (nmCRPC state) [b]				
Apalutamide	50%	10.97	£8,919.27	
Darolutamide	50%	4.93	£13,175.09	

ARI	Proportion	Duration (cycle)	Cost (£/cycle)	One-off Cost (£)
nmCRPC subsequent treatment cost				£81,405.91
Metastatic cancer-resistant prostate cancer (mCRPC state)				
Enzalutamide	16.67% [a]	6.07[a]	£8,919.27 [a]	
Abiraterone	16.67% [a]	8.40 [a]	£8,919.27 [a]	
Docetaxel	16.67% [a]	4.37 [a]	£1,316.42 [a]	
Radium-223	16.67% [a]	1.84 [a]	£15,606.97 [a]	
Cabazitaxel with prednisolone	16.67% [a]	2.21 [a]	£1,997.18 [a]	
Dexamethasone	16.67% [a]	1.50 [a]	£7.82 [a]	
nmCRPC subsequent treatment cost (one-off)				£83,963.69

Source: CS Appendix O.1.10 Tables 134 and 135 (duration and proportion), and CS Appendix Q Table 144 (cost)
ADT: androgen deprivation therapy, ARI: androgen receptor inhibitors
[a] mCRPC proportion, duration and cost are equal for the first, second and third lines.
[b] The original ARI proportion included enzalutamide as treatment.

4.2.8.5 Health state cost and resource use

Health state costs were categorised as professional and social services, health care professionals, hospital resource use, and treatment follow-up. The cost was taken from the NHS National Cost Collection[68]. The resource used was taken from a survey of clinicians reported in the company submissions for NICE TA580[13] (Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer) for the non-metastatic health states and NICE TA712[14] (Enzalutamide for treating hormone-sensitive prostate cancer) and NICE TA377 [70] (Enzalutamide in pre-chemo metastatic hormone-resistant prostate cancer) for the metastatic health states. The detailed frequency of resource use and its costs were shown in CS Appendix Q.1.4. Table 146 for the non-metastatic health state and Table 147 for the metastatic health state.

In response to clarification question B17, the company amended in CS Appendix Q.1.4 Table 147 the percentage of patients needing a “Radiographic or MRI scan” service during the follow-up period from 50% to 5% to correspond with the estimate from the NICE TA580[13] and NICE TA712[14]. Therefore, the cost of follow-up for the metastatic health state was updated from £242.45 to £203.81 per month. The cost of follow-up for the non-metastatic health state remains £251.94 per month.

The Clinical advice to the EAG suggested differences in the frequency of investigations as follows: metastatic patients should receive a full blood count, liver function test, kidney function test and PSA every 12 weeks rather than eight weeks, although there is some variation around this as clinically indicated. The EAG assessed the 12-week frequency for the mentioned follow-up exams in a scenario analysis, and there was a marginal difference in the results (see section 6.1).

4.2.8.6 Adverse Event costs

Adverse event costs are calculated by multiplying the total frequency of the adverse events by the unit cost. The costs are applied as a one-off in the first treatment cycle only. There are two groups of adverse event costs: MACE and non-MACE events.

In CS Appendix Q.1.3 Table 145, the company provided MACE's one-off acute care and chronic costs for fatal and nonfatal events. The nonfatal events costs were based on the literature (Danese et al. 2016 for nonfatal myocardial infarction (MI) and other CV events, and Xu et al. 2018 for nonfatal stroke)[71 72]. All fatal costs were from the NHS Cost Collection[68], adjusted by inflation. In response to the clarification question B12, the company amended these fatal costs for acute MACE events ("Fatal MI", "Fatal Stroke", and "Other Fatal CV") from £1005.00 to £879.24.

The costs of treatment of adverse events other than MACE were taken from the NHS Collection Cost 2019/2020[73] and are available in CS Table 52. Hot flush was considered to have no cost and was based on the same assumption made in NICE TA712.[14]

4.2.8.7 End of life costs

The company's model includes a cost of £7,071 for end-of-life care for deaths related to advanced prostate cancer. This was based on an estimate of costs of care in the last eight weeks of life for people with cancer from a King's Fund report by Addicott and Dewar (2008) [74] (£5,324), that the company uprated to 2021/22 prices.[75] However, the Addicott and Dewar estimate was based on a small sample; and it is now very out of date. The EAG considers that the best available source for end of life health and social care costs for cancer is a Nuffield Trust report by Georghiou et al. (2012)[76], reported at 2021/22 prices in the PSSRU Unit Costs of Health and Social Care 2022 manual: £13,113.[75]

Table 33 End of life cost for health and social care

Source	Cost £ per person in final year of life	
	Original estimate	2021/22 prices

Source	Cost £ per person in final year of life	
Addicott and Dewar 2008[74] (£5,324 at 2008/2009 prices)	£5,324, 2008/9 prices	£7,071
Georghiou et al. 2012[76]	£10,844, 2010/11 prices	£13,113

EAG conclusion on resource use and costs

The company's approach to estimating resources and costs in the economic model is consistent with the NICE reference case and previous technology appraisals for prostate cancer.

The EAG identified some errors in the calculation of adverse events costs (fatal MACE events), administration costs (intravenous administration), resource use (percentage of patients needing a "Radiographic or MRI scan"), and selection of drug acquisition costs (docetaxel and cabazitaxel, from BNF to eMIT prices). We also consider that end-of-life care costs in the company's model are underestimated. Moreover, the EAG observed two errors in the economic model in the subsequent treatment calculation (see discussion in section 5.5.2).

We have assessed the impact of uncertainty over the relative use of ARI therapies in subsequent treatment costs in two scenarios, varying the proportions to select the most (and the least) expensive treatments for each CRPC health state (see section 6.3).

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company reported their original deterministic base case results in CS Table 55, with an ICER of £9,489 per QALY gained. This and all other cost-effectiveness results in this report are conducted with a confidential patient access scheme (PAS) price discount for relugolix. The company made corrections to their model in response to clarification questions. Revised deterministic base case results are reported below, with an ICER of £10,751 per QALY gained. In addition, the company provide the pairwise cost-effectiveness results, reported in Table 35 below.

Table 34 Cost-effectiveness results: company base case (deterministic)

Technology	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	(£/QALY)
Original company submission							
GnRH agonists	[redacted]	[redacted]	[redacted]				£9,489
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Revised in response to clarification questions							
GnRH agonists	[redacted]	[redacted]	[redacted]				£10,751
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from CS Table 55 and clarification questions
Abbreviations: LYG, life-years gained; QALYs, quality-adjusted life years, ICER, incremental cost effectiveness ratio.

Table 35 Pairwise cost-effectiveness results: company base case

Technology	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	(£/QALY)
Relugolix	[redacted]	[redacted]			
Triptorelin (cheapest)	[redacted]	[redacted]	[redacted]	[redacted]	£11,457
Goserelin (most expensive)	[redacted]	[redacted]	[redacted]	[redacted]	£10,024

Source: Reproduced from company's clarification response.
Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost effectiveness ratio.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company report their original deterministic sensitivity analysis results for the 15 most influential parameters in Figure 5 of the clarification response. The ranges of variation for the input parameters were based on +/- 25% of base case estimates. The company's results indicate that the parameters relating to health state utilities for biochemical relapse were the main drivers for the model, reducing the NMB to [redacted] at a WTP threshold of £20,000 per QALY in the BR on/off treatment sub-health states.

Figure 8 Deterministic sensitivity analysis tornado diagram

Source: company clarification response Figure 5

5.2.2 Probabilistic sensitivity analysis (PrSA)

The company conducted a probabilistic sensitivity analysis (PrSA) with input parameter distributions as presented in CS Appendix N. The PrSA was run for 500 iterations. The cost-effectiveness plane and cost-effectiveness acceptability curve are shown in Figure 9 and Figure 10 below, respectively. The probabilistic results were in line with the deterministic results when run by the EAG (see Table 36).

Table 36 Probabilistic sensitivity analysis results

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Company base case					
GnRH agonists	[redacted]	[redacted]			£10,751

Technology	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	(£/QALY)
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	
Probabilistic sensitivity analysis					
GnRH agonists	[redacted]	[redacted]			£11,090
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: LYG, life-years gained; QALYs, quality-adjusted life years, ICER, incremental cost effectiveness ratio.

Figure 9 Relugolix cost-effectiveness plane

Source: company clarification response Figure 6

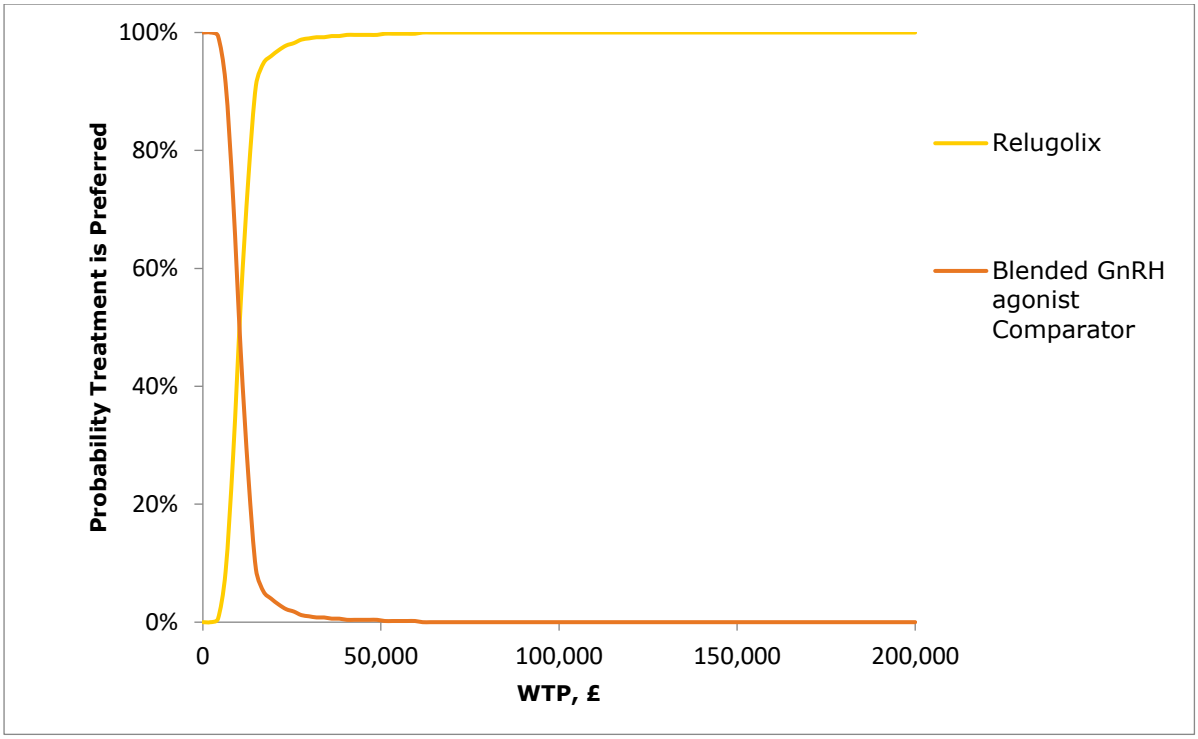


Figure 10 Relugolix cost effectiveness acceptability curve (CEAC)

Source: company's economic model

5.3 Company's scenario analyses

The company included four scenarios in their submission:

- **Carry-over period of MACE:** two scenarios testing no carry over period (0 months) and one year carry over period (12 months)
- **Adverse event disutility:** scenario excluding the injection site disutility
- **ADT treatment continuation after castration resistance:** Patients do not receive **initial** ADT after becoming castrate resistant. The patient will receive another ADT, represented by an ADT mix, with cost as the mean cost of all ADTs in this company submission.
- **ADT treatment effect on MACE incidence:** scenario considering no incidence of MACE ("relative risk of MACE given prior to MACE" equal to one, no carry over period (duration equal to zero), and "risk of MACE for LHRH agonists without prior MACE" equal to zero).

The company's economic model has a scenario module with 12 additional scenarios:

- **Risk of PSA progression – PSA PFS mHSPC:** scenario with Lognormal distribution (best-fitting distribution) instead of Weibull distribution (third best-fit distribution and best long term projections of PSA PFS).
- **Percent LA/BR patients discontinuing ADT:** scenario percentage of LA/BR patients discontinuing ADT considering expert opinion instead of the Myovant analysis
- **Utility values from HERO trial:** scenario with utility values based on NICE TA404 (degarelix)
- **History of MACE estimates:** scenario with estimates from Brady 2020 ("Risk of MACE for LHRH agonists" = 0.094 (no change), prior MACE and no prior MACE initial probabilities with higher values for the no prior MACE LA/BR health states).
- **MACE estimates from Zhang 2021:** scenario with relative risk of MACE for relugolix and degarelix equal to 0.7 (base case RR: 0.38)
- **MACE estimates from Margel 2019:** scenario with relative risk of MACE for relugolix and degarelix equal to 0.150 (base case RR: 0.38) and risk of MACE for LHRH agonists equal to 0.20 (base case: 0.094).
- **Risk of MACE from the HERO trial:** risk of MACE for LHRH agonists equal to 0.045 (base case : 0.094)
- **Risk of MACE from Margel (2019), MACE RR from Shore (2020):** risk of MACE for LHRH agonists equal to 0.2 (base case: 0.094), relative risks remain the same.
- **Risk of MACE from HERO CSR, MACE RR from Margel (2019):** scenario with relative risk of MACE for relugolix and degarelix equal to 0.150 (base case RR: 0.38) and risk of MACE for LHRH agonists equal to 0.045 (base case: 0.094).
- **History of MACE and RR of MACE from Albertsen, 2014:** scenario with relative risk of MACE for relugolix and degarelix equal to 0.440 (base case RR: 0.38), and initial probability for LA/BR for prior MACE and no prior MACE with slightly different probabilities.
- **Unadjusted history of MACE from Albertsen (2014):** only the initial probability for LA/BR for prior MACE and no prior MACE with slightly different probabilities from the previous scenario
- **Patients without castration at increased risk of PSA progression:** PSA PFS LA/BR hazard ratio (HR) treatment specific equal to 1.65 (base case: 1.0), HR off treatment equal to 6.061 (base case: 10), HR for castrate equal to 0.606 (base case: 1.0). PSA PFS for mHSPC hazard ratio for treatment specific equal to 1.650 (base case: 1.0), and HR castrate equal to 0.606 (base case: 1.0).

Appendix 3 Table 46 shows the MACE parameters values used in the company's scenarios above. The scenario results are shown in Table 37.

Table 37 Company scenario analyses

Base Case	Scenario	Treatment	Total Cost (£)	Total QALYs	ICER (£/QALY)
Company's revised base case		GnRH agonists	[redacted]	[redacted]	£10,751
		Relugolix	[redacted]	[redacted]	
Company's scenarios analysis presented in the submission					
Carry-over period of MACE – 6.8 months	0 months	GnRH agonists	[redacted]	[redacted]	£11,209
		Relugolix	[redacted]	[redacted]	
	12 months	GnRH agonists	[redacted]	[redacted]	£10,714
		Relugolix	[redacted]	[redacted]	
Adverse event disutility - Include	Exclude AE disutility	GnRH agonists	[redacted]	[redacted]	£10,751
		Relugolix	[redacted]	[redacted]	
ADT treatment continuation after castration resistance	Patients do not receive **initial** ADT after becoming castrate resistant	GnRH agonists	[redacted]	[redacted]	£10,546
		Relugolix	[redacted]	[redacted]	
ADT treatment effect on MACE incidence	No treatment effects on MACE incidence	GnRH agonists	[redacted]	[redacted]	Dominated
		Relugolix	[redacted]	[redacted]	
Additional company's scenarios (only in the economic model)					
Risk of PSA progression – PSA PFS mHSPC distribution Weibull model	PSA PFS mHSPC distribution: Lognormal model	GnRH agonists	[redacted]	[redacted]	£10,685
		Relugolix	[redacted]	[redacted]	
Percentage of discontinuation LA/BR based on Myovant study	Percentage of discontinuation LA/BR based on KOL	GnRH agonists	[redacted]	[redacted]	£10,932
		Relugolix	[redacted]	[redacted]	
Utility values based on HERO trial	Utility values based on TA404 (degarelix)	GnRH agonists	[redacted]	[redacted]	£10,656

Base Case	Scenario	Treatment	Total Cost (£)	Total QALYs	ICER (£/QALY)
		Relugolix	[redacted]	[redacted]	
History of MACE from Albertsen (2014)	History of MACE estimates from Brady 2020	GnRH agonists	[redacted]	[redacted]	£9,765
		Relugolix	[redacted]	[redacted]	
Relative risk of MACE from HERO trial	MACE RR estimates from Zhang 2021	GnRH agonists	[redacted]	[redacted]	£11,337
		Relugolix	[redacted]	[redacted]	
	MACE RR estimates from Margel 2019	GnRH agonists	[redacted]	[redacted]	£10,742
		Relugolix	[redacted]	[redacted]	
Risk of MACE from Brady 2020	Risk of MACE from the HERO trial	GnRH agonists	[redacted]	[redacted]	£10,561
		Relugolix	[redacted]	[redacted]	
Risk of MACE from Brady 2020, relative risk from HERO trial	Risk of MACE from Margel 2019, MACE RR from Shore 2020	GnRH agonists	[redacted]	[redacted]	£11,070
		Relugolix	[redacted]	[redacted]	
Risk of MACE from Brady 2020, relative risk from HERO trial	Risk of MACE from HERO CSR, MACE RR from Margel (2019)	GnRH agonists	[redacted]	[redacted]	£10,210
		Relugolix	[redacted]	[redacted]	
History of MACE from Albertsen (2014) and RR of MACE from HERO trial	History of MACE and RR of MACE from Albertsen, 2014	GnRH agonists	[redacted]	[redacted]	£10,821
		Relugolix	[redacted]	[redacted]	
History of MACE from Albertsen (2014)	Unadjusted history of MACE from Albertson (2014)	GnRH agonists	[redacted]	[redacted]	£10,734
		Relugolix	[redacted]	[redacted]	
Patients without castration have the same risk as patients with castration	Patients without castration are at increased risk of PSA progression	GnRH agonists	[redacted]	[redacted]	£9,339
		Relugolix	[redacted]	[redacted]	

Source: Reproduced from CS Table 58 and company's economic model. Abbreviations: QALY, quality adjusted life-year; ICER. Incremental cost-effectiveness ratio; MACE, major cardiovascular events; AE, adverse events; ADT, androgen deprivation therapy; PSA, prostate-specific antigen; PFS, progression free survival; RR, relative risk; LA, locally advanced; BR, biochemical relapse.

5.4 Subgroup analyses

The company performed subgroup analysis on degarelix for patients with spinal metastases. The population comprised mHSPC patients. The company also provided subgroup analyses for the locally advanced and biochemical relapse subgroups in the updated clarification response. Table 38 below reports the results.

Table 38 Subgroups analyses: LA, BR and mHSPC

Subgroup	Treatment	Total Cost (£)	Total QALYs	Pairwise ICERs (£/QALY)
Company's base case	Relugolix	[redacted]	[redacted]	
	GnRH agonists	[redacted]	[redacted]	£10,751
	Triptorelin (cheapest)	[redacted]	[redacted]	£11,457
	Goserelin (most expensive)	[redacted]	[redacted]	£10,024
Locally advanced HSPC (LA)	Relugolix	[redacted]	[redacted]	
	GnRH agonists	[redacted]	[redacted]	£11,022
	Triptorelin (cheapest)	[redacted]	[redacted]	£11,594
	Goserelin (most expensive)	[redacted]	[redacted]	£10,434
Biochemical relapse (BR)	Relugolix	[redacted]	[redacted]	
	GnRH agonists	[redacted]	[redacted]	£10,920
	Triptorelin (cheapest)	[redacted]	[redacted]	£11,491
	Goserelin (most expensive)	[redacted]	[redacted]	£10,331
Metastatic (mHSPC)	Relugolix	[redacted]	[redacted]	
	GnRH agonists	[redacted]	[redacted]	£9,632
	Triptorelin (cheapest)	[redacted]	[redacted]	£11,226
	Goserelin (most expensive)	[redacted]	[redacted]	£7,989
	Degarelix	[redacted]	[redacted]	£60,626 [a]

Source: Reproduced from clarification response update Table 15, Table 16, and Table 17.
Abbreviations: QALY, quality adjusted life-year; ICER. Incremental cost-effectiveness ratio; LA, locally advanced; BR, biochemical relapse.
[a] South west quadrant: Relugolix less expensive and less effective than degarelix

5.5 Model validation and face validity check

We conducted a range of checks on the company's model using an EAG checklist:

- Input checks: comparison of all parameter values in the model against the values stated in the company submission and cited sources.

- Output checks: replication of results reported in the company submission using the company model.
- 'White box' checks: manual checking of formulae working from the Markov cohort model, which includes reviewing the calculations across each cycle and working backwards to trace links to input parameters and forwards to the results.
- 'Black box' checks: working through a list of tests to assess whether changes to key model inputs or assumptions have the expected effects on the model results.

The EAG found it difficult to validate the numerous tunnel states in the model, as noted in Section 4.2.2. The EAG found some inconsistencies in the company submission and the original economic model and inquired about these discrepancies in the clarification questions. The company responded with modifications to the economic model, as outlined in Section 5.5.1 below.

5.5.1 Company corrections to the model

The following corrections were made by the company to their original model:

- The percentage of patients with sustained testosterone suppression to castrate levels with relugolix in the model was changed from 96.792% to 96.7% in line with the value reported in the Shore et al. 2020 paper (clarification question B4).
- The company originally implemented general population utility norms for age adjustment using utilities reported in Kind et al. 1999. However, more recent utility estimates are available, and the company updated their economic model to use the equation provided by Ara and Brazier 2010 (clarification question B8)
- The company adjusted the baseline utility values in the economic model to be consistent with general population norms (clarification question B9).
- The company corrected the adverse event utility for injection site reaction in the model, where the original model had a disutility of zero instead of a disutility value of -0.011, as reported in CS Table 51 (clarification question B10).
- The company updated the costs for MACE events using NHS reference costs 2021/22; the original costs were taken from NHS reference costs 2019/20. As a result, the amended costs for MACE events in the updated model is £879.24 (clarification question B12).
- The company amended the list prices for docetaxel and cabazitaxel using eMIT prices in place of BNF prices, with costs of £16.04 and £172.09, respectively (clarification question B13).

- The company updated the daily dose for radium-223 from 1.35mci to 1.49mci (clarification question B14).
- The company corrected the weighted average for intravenous administration costs from £362 to £286.71, using the NHS reference costs 2021/22 (clarification question B16).
- The company corrected the percentage of patients requiring a radiographic or MRI scan during follow-up, where a value of 50% was erroneously reported in CS B.3.5.2. The correct value, 5%, was implemented in the economic model (clarification question B17).
- The original company model did not use the administration costs for subsequent treatments. The company updated the model to include both administration and dispensing costs for subsequent treatments.

5.5.2 EAG corrections to the company model

- There are some errors we identified that had an impact on the company's base case results:
- The one-off subsequent treatment cost for the nmCRPC state was calculated by multiplying the drug costs (£ per model cycle) by duration in months (SubTxCalc sheet, cells AH12 to AH16). However, duration should be in model cycles (3 months), not in months.
- There is no evidence of drug wastage coded in the model for medications administered via IV injections, as was stated in CS B.3.5.1.6. In SubTxCalc, cells N16 to N19, if the calculated number of vials needed for a dose is a fraction, the number of vials must be rounded up.
- We corrected the calculation of the annual probability of MACE for patients with no prior MACE treated with leuprolide based on the Brady et al. analysis of claims data (CS O.1.9). Cell MACE_Incidence!E12 should be 10.08% (instead of 9.39%) (see section 4.2.6.2.2 above). The impact on the ICER is negligible.
- The EAG observed a discrepancy in the cost of the ADT mix calculation, in which the average cost of relugolix, leuprorelin, goserelin, and triptorelin is £204.47 instead of the value defined in the company submission of £197.43 (see section 4.2.8.4 above).

The EAG re-ran the analyses with the corrected formulas. These changes, added to the company's corrections, decreased the base case ICER from £10,751 (company's base case) to £7,870 per QALY (see Table 39).

Table 39 Cost-effectiveness results from the EAG corrections to the company model

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Company base case					
GnRH agonists	[redacted]	[redacted]			
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	£10,751
EAG corrections to the company base case					
GnRH agonists	[redacted]	[redacted]			
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	£7,870

Abbreviations: LYG, life-years gained; QALYs, quality-adjusted life years, ICER, incremental cost effectiveness ratio.

5.6 EAG summary of key issues and additional analyses

We summarise and critique key assumptions in the company's model in Table 45 in Appendix 2.

6 EAG ADDITIONAL ANALYSIS

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Based on the EAG critique of the company's model assumptions (Table 45), we performed a range of additional scenario analyses on the following model assumptions:

- Use the end-of-life cost from Georghiou 2012 (section 4.2.8.7)
- Use the prevalence of prior MACE at baseline from the HERO trial (section 4.2.3)
- Exclude enzalutamide as a treatment for nmCRPC (section 4.2.8.4)
- Vary subsequent treatment costs considering the least expensive ARI (see section 4.2.8.4, expert comment): 100% apalutamide for nmCRPC, and docetaxel, cabazitaxel with prednisolone, and dexamethasone for mCRPC (33.3% each).
- Vary subsequent treatment costs considering the most expensive ARI (see section 4.2.8.4, expert comment): 100% darolutamide for nmCRPC, and radium-223, enzalutamide and abiraterone for mCRPC (33.3% each).
- Use the relative risk of MACE from the sensitivity analysis of MACE (CS Table 39, scenario 1) and from Cirne et al. 2022 (scenario 2), and RR = 1 (scenario 3, no treatment effect).
- Vary the treatment-specific hazard ratio for the PSA PFS (LA/BR HSPC): (HR=2) and (HR=0.5).
- Vary the hazard ratio off treatment vs on treatment for the PSA PFS (LA/BR HSPC): (HR=1 (on treatment) /20 (off treatment))
- Vary the treatment-specific hazard ratio for MFS (LA/BR HSPC): HR=10
- Vary the proportion of fatal versus non-fatal MACE events (see section 4.2.6.2.3 Table 25): evaluate the percentage of fatal MACE events in scenarios with 15% and 40% fatality with MACE events (company's base case: 27%).

The ICERs range from £6,271 per QALY (scenario varying the proportion of fatal versus non-fatal MACE to 15%) to £17,523 per QALY (scenario varying the treatment-specific hazard ratio for the PSA PFS (LA/BR HSPC) from HR=1 to HR=2). In one scenario, Relugolix is dominated (no treatment effect in MACE, RR = 1)

- The EAG tested an additional group of scenarios, resulting in a slight difference in the ICER compared with the company's revised case (less than £200):

- Vary the frequency of follow-up exams (expert comment, section 4.2.8.5): metastatic patients should receive a full blood count, liver function test, kidney function test and PSA every 12 weeks rather than eight weeks (ICER: £10,729, difference: £22).
- Use the percentage of castration from the NMA (Table 22) for testosterone suppression (ICER: £10,751, no difference)
- Use Weibull distribution for the MFS nmCRPC (pessimistic) (ICER: £10,863, difference: £112)
- Vary the treatment-specific hazard ratio for OS mHSPC (base case HR =0.4): Treatment-specific HR = 0.2 (ICER: £10,833, difference: £82); Treatment-specific HR=0.8 (ICER: £10,636, difference: -£115); Treatment-specific HR=1 (ICER: £10,596, difference: -£155)
- Use the lognormal distribution for the OS mCRPC (best fit): (ICER: £10,626, difference: -£125); and Weibull distribution (ICER: £10,827, difference: £76)
- Use the lognormal distribution for the PSA mHSPC (best fit) (ICER: £10,685, difference: -£66)
- Use the generalised gamma distribution for the PSA mHSPC(most optimistic) (ICER: £10,578, difference: -£173)

6.2 EAG's preferred assumptions

Based on the EAG critique of the company's model discussed in Table 45, we have identified four key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- Exclude enzalutamide from the subsequent treatment for nmCRPC (see TA580). In addition, we adjusted the proportion to 50% of apalutamide and 50% of darolutamide to attend to all patients in the nmCRPC state.
- Use the HERO trial as a source for the prevalence of prior MACE at baseline instead of Albertsen 2014 (see section 4.2.3 Population)
- Apply end-of-life cost from Georghiou 2012 [76]
- Remove the assumed carry-over period for MACE after discontinuation of GnRH agonists.

Table 40 shows the cumulative cost-effectiveness of applying the EAG preferred model assumptions to the company's revised base case. The ICER decreased from £10,751 to £9,990 per QALY. There was a decrement from the company's revised base case (£10,751) to the EAG correction to the company's base case (£7,870). The EAG key assumptions

increased the ICER from the EAG's corrections to the company's base case, from £7,870 to £9,990 per QALY.

Table 40 EAG's preferred model assumptions: cumulative change to ICER

Preferred assumption	Treatment	Total Costs	Total QALYs	Cumulative ICER £/QALY
Company's revised base case	GnRH agonists	[redacted]	[redacted]	£10,751
	Relugolix	[redacted]	[redacted]	
+ EAG corrections to the company's revised base case (section 5.5.2)	GnRH agonists	[redacted]	[redacted]	£7,870
	Relugolix	[redacted]	[redacted]	
+ Exclude enzalutamide as a treatment for nmCRPC (section 4.2.8.4)	GnRH agonists	[redacted]	[redacted]	£8,088
	Relugolix	[redacted]	[redacted]	
+ prevalence of prior MACE at baseline from HERO trial (section 4.2.3)	GnRH agonists	[redacted]	[redacted]	£8,364
	Relugolix	[redacted]	[redacted]	
+ end-of-life cost from Georghiou 2012 (section 4.2.8.7)	GnRH agonists	[redacted]	[redacted]	£9,382
	Relugolix	[redacted]	[redacted]	
+exclude carry-over period for MACE	GnRH agonists	[redacted]	[redacted]	£9,990
	Relugolix	[redacted]	[redacted]	
EAG base case	GnRH agonists	[redacted]	[redacted]	£9,990
	Relugolix	[redacted]	[redacted]	

Source: Produced by the EAG from the company's model

Appendix 2 presents some graphs comparing the company's base case results and the EAG base case results.

We reran the probabilistic sensitivity analysis (PrSA) with the EAG base case model. The cost-effectiveness scatterplot is shown in Figure 11. The probabilistic results were in line with the deterministic results (see Table 41).

Table 41 Probabilistic sensitivity analysis results – EAG Base case

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Company base case					
GnRH agonists	[redacted]	[redacted]			£9,990
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	
Probabilistic sensitivity analysis					
GnRH agonists	[redacted]	[redacted]			£10,223
Relugolix	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: LYG, life-years gained; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

[redacted]

Figure 11 Relugolix cost-effectiveness plane using EAG base case model

6.3 Scenario analyses conducted with the EAG's preferred assumptions

We performed a range of scenario analyses with the EAG base case to analyse the impact of changing some of the model assumptions in the final cost-effectiveness results. The scenarios in Table 42 are divided into three groups:

- Selection of scenarios from the EAG exploratory scenarios in section 6.1
- The company's preferred assumptions that were modified in the EAG base case (section 6.2)
- Selection of the company's scenarios in section 5.3 that had more than 3% difference in the ICER (results in Table 37)

These scenarios are previously described in sections 6.1, 6.2, and 5.3.

Table 42 EAG Scenarios with the EAG preferred base case below summarises the results of the scenarios on the EAG base case. The scenarios that have the most significant effect on the cost-effectiveness are:

- Varying the subsequent treatment costs increases the ICER by £3,555 per QALY for the scenarios with the most expensive ARI treatments. It decreases the ICER by £3,587 per QALY in the scenario with the least expensive ARI treatments.
- Varying the proportion of fatal versus non-fatal MACE events decreases the ICER by £4,298 to 15% fatality with MACE events and increases the ICER by £2,344 to 40% fatality with MACE events.
- Using the relative risk of MACE from the sensitivity analysis of MACE (CS Table 39, scenario 1) increases the ICER by £1,367 per QALY.
- Using the end-of-life costs from Addicott et al. 2008 decreases the ICER by £1,073.
- Considering that patients do not receive initial ADT after becoming castrate-resistant but continue with an ADT mix decreases the ICER by £1,300.
- In the scenario assuming no treatment effect on MACE (RR = 1), relugolix was dominated in the EAG base case model.

The ICER varied less than 5% per QALY in the other scenarios.

Table 42 EAG Scenarios with the EAG preferred base case

Base Case	Scenario	Treatment	Total Cost (£)	Total QALYs	ICER (£/QALY)
EAG base case		GnRH agonists	[redacted]	[redacted]	£9,990
		Relugolix	[redacted]	[redacted]	
EAG Scenarios with the EAG base case model					
Testosterone suppression – % castrate from HERO trial	% castrate from NMA	GnRH agonists	[redacted]	[redacted]	£9,990
		Relugolix	[redacted]	[redacted]	
RR of MACE from HERO trial	RR of MACE from Table 25 (NMA Sensit. Analysis)	GnRH agonists	[redacted]	[redacted]	£11,357
		Relugolix	[redacted]	[redacted]	
	RR of MACE incidence from Cirne et al. 2022	GnRH agonists	[redacted]	[redacted]	£10,287
		Relugolix	[redacted]	[redacted]	
	RR of MACE from Table 25 (NMA Primary)	GnRH agonists	[redacted]	[redacted]	£10,046
		Relugolix	[redacted]	[redacted]	
	RR of MACE equal to 1	GnRH agonists	[redacted]	[redacted]	Dominated
		Relugolix	[redacted]	[redacted]	
Subsequent treatment costs	Only the most expensive ARIs: darolutamide for nmCRPC and radium-223, enzalutamide and abiraterone for nmCRPC (33.3% each)	GnRH agonists	[redacted]	[redacted]	£13,545
		Relugolix	[redacted]	[redacted]	
	Only the least expensive ARIs: 100% apalutamide for nmCRPC, and docetaxel,	GnRH agonists	[redacted]	[redacted]	£6,403
		Relugolix	[redacted]	[redacted]	

Base Case	Scenario	Treatment	Total Cost (£)	Total QALYs	ICER (£/QALY)
	cabazitaxel with prednisolone, and dexamethasone for mCRPC (33.3% each)				
Proportion of fatal versus non-fatal MACE: 27%	Proportion of fatal versus non-fatal MACE: 15%	GnRH agonists	[redacted]	[redacted]	£5,692
		Relugolix	[redacted]	[redacted]	
	Proportion of fatal versus non-fatal MACE: 40%	GnRH agonists	[redacted]	[redacted]	£12,334
		Relugolix	[redacted]	[redacted]	
Company's assumptions using the EAG base case model					
End-of-life costs from Georghiou 2012	End-of-life costs from Addicott et al. 2008	GnRH agonists	[redacted]	[redacted]	£8,917
		Relugolix	[redacted]	[redacted]	
Prevalence of prior MACE at baseline from HERO trial	Prevalence of prior MACE from Albertsen 2014	GnRH agonists	[redacted]	[redacted]	£9,689
		Relugolix	[redacted]	[redacted]	
No Carry-over period for risk of MACE	Carry-over period of 6.8 months	GnRH agonists	[redacted]	[redacted]	£9,382
		Relugolix	[redacted]	[redacted]	
Company's scenarios using the EAG base case model					
ADT treatment continuation after castration resistance	Patients do not receive initial ADT after becoming castrate resistant	GnRH agonists	[redacted]	[redacted]	£8,690
		Relugolix	[redacted]	[redacted]	
Risk of PSA progression – PSA PFS mHSPC: Weibull distribution	Risk of PSA progression – PSA PFS mHSPC: lognormal distribution	GnRH agonists	[redacted]	[redacted]	£9,940
		Relugolix	[redacted]	[redacted]	

Source: Produced by the EAG from the company's model

6.4 Subgroup analysis conducted with the EAG's preferred assumptions

Section 5.4 detailed the subgroup analysis on degarelix for patients with spinal metastases and the subgroup analyses for the locally advanced and biochemical relapse subgroups. Table 43 below replicated these subgroups results using the EAG base case model.

Table 43 Subgroup analysis EAG preferred assumptions

Subgroup	Treatment	Total Cost (£)	Total QALYs	Pairwise ICERs (£/QALY)
EAG base case	Relugolix	[redacted]	[redacted]	
	GnRH agonists	[redacted]	[redacted]	£9,990
	Triptorelin (cheapest)	[redacted]	[redacted]	£10,766
	Goserelin (most expensive)	[redacted]	[redacted]	£9,190
Locally advanced HSPC (LA)	Relugolix	[redacted]	[redacted]	
	GnRH agonists	[redacted]	[redacted]	£9,425
	Triptorelin (cheapest)	[redacted]	[redacted]	£10,077
	Goserelin (most expensive)	[redacted]	[redacted]	£8,754
Biochemical relapse (BR)	Relugolix	[redacted]	[redacted]	
	GnRH agonists	[redacted]	[redacted]	£9,425
	Triptorelin (cheapest)	[redacted]	[redacted]	£10,077
	Goserelin (most expensive)	[redacted]	[redacted]	£8,754
mHSPC with/without degarelix	Relugolix	[redacted]	[redacted]	
	GnRH agonists	[redacted]	[redacted]	£12,702
	Triptorelin (cheapest)	[redacted]	[redacted]	£14,162
	Goserelin (most expensive)	[redacted]	[redacted]	£11,198
	Degarelix	[redacted]	[redacted]	£58,950 [a]

Source: Produced by the EAG from an adapated version of the company's model

6.5 [a] South west quadrant: Relugolix less expensive and less effective than degarelixConclusions on the cost effectiveness evidence

The key issues identified by the EAG in the cost-effectiveness evidence are the following:

- Spinal metastases subpopulation
- High-risk localised subpopulation
- Treatment effects on MACE incidence

The EAG identified a set of alternative clinical assumptions and input parameter values to those of the company and we have incorporated these into the EAG base case. All of them are described in Appendix 2, Table 45.

The EAG's preferred model assumptions decreased the ICER for Relugolix versus blended comparators to £9,990 per QALY. The overall results are most sensitive to changes in the subsequent treatment costs, the proportion of fatal versus non-fatal MACE events, the relative risk of MACE, interrupting the initial ADT after PSA progression and continuing with an ADT mix, and the end-of-life costs.

7 REFERENCES

1. England RCoSo. National Prostate Cancer Audit: State of the Nation Report. London, 2024.

2. Support MC. Causes and risk factors of prostate cancer 2021 [Available from: https://www.macmillan.org.uk/cancer-information-and-support/prostate-cancer/causes-and-risk-factors-of-prostate-cancer accessed 19 March 2024 2024.

3. National Institute for H, Care E. Prostate cancer: diagnosis and management (NG131) 2019 [Available from: https://www.nice.org.uk/guidance/ng131.

4. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *Journal of the National Cancer Institute* 2010;102(1):39-46.

5. O'Farrell S, Garmo H, Holmberg L, et al. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2015;33(11):1243-51.

6. Moul JW. The evolving definition of advanced prostate cancer. *Reviews in urology* 2004;6(Suppl 8):S10.

7. National Institute for H, Care E. Degarelix for treating advanced hormone-dependent prostate cancer (TA404) 2016 [accessed [Available at: https://www.nice.org.uk/guidance/ta404; Accessed on January 3, 2021.

8. Limited AU. Summary of Product Characteristics Zoladex 3.6mg Implant 2023 [Available from: https://www.medicines.org.uk/emc/product/1543/smpc accessed 20 March 2024.

9. Limited I. Summary of Product Characteristics Decapeptyl SR 11.25mg (triptorelin pamoate) 2024 [Available from: https://www.medicines.org.uk/emc/product/780/smpc accessed 20 March 2024.

10. Ltd NH. Summary of Product Characteristics Suprefact Injection 2022 [Available from: https://www.medicines.org.uk/emc/product/11242/smpc accessed 20 March 2024.

11. Ltd TU. Summary of Product Characteristics Prostap 3 DCS 2023 [Available from: https://www.medicines.org.uk/emc/product/4651/smpc accessed 20 March 2024.

12. European Society for Medical O. Clinical Practise Guidelines-Prostate Cancer [Available from: https://www.esmo.org/guidelines/guidelines-by-topic/genitourinary-cancers/prostate-cancer.

13. National Institute for H, Care E. Enzalutamide for hormone-relapsed non-metastatic prostate cancer (TA580) 2019 [accessed [Available at: https://www.nice.org.uk/guidance/ta580/history; Accessed on: January 22, 2021.

14. National Institute for H, Care E. Enzalutamide for treating hormone-sensitive metastatic prostate cancer (TA712) 2021 [Available from: https://www.nice.org.uk/guidance/ta712/evidence/committee-papers-pdf-9191003869.

15. Excellence NIfHaC. Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer (TA741) 2021 [Available from: https://www.nice.org.uk/guidance/ta741 accessed 20 March 2024.

16. Excellence NIfHaC. Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer (TA903) 2023 [Available from: https://www.nice.org.uk/guidance/ta903 accessed 20 March 2024.

17. Chaimani A, Caldwell DM, Li T, et al. Undertaking network meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions2019:285-320.

18. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *New England Journal of Medicine* 2020;382(23):2187-96. doi: http://dx.doi.org/10.1056/NEJMoa2004325

19. Ruikar V. Interactive Voice/Web Response System in clinical research. *Perspect Clin Res* 2016;7(1):15-20. doi: 10.4103/2229-3485.173781

20. Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU international* 2008;102(11):1531-38.

21. Heyns CF, Simonin MP, Grosgurin P, et al. Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. *BJU international* 2003;92(3):226-31.

22. Silva ÉD, Ferreira U, Matheus W, et al. Goserelin versus leuprolide in the chemical castration of patients with prostate cancer. *International urology and nephrology* 2012;44:1039-44.

23. Tanaka N, Fujimoto K, Hirao Y, et al. Endocrine response to a single injection of goserelin 3.6 mg or leuprolide 3.75 mg in men with prostate cancer. *Archives of Andrology* 2007;53(5):289-93.

24. Clinicaltrials.gov. A Phase 2 study to evaluate the safety and efficacy of TAK-385, together with a leuprorelin observational cohort, in participants with prostate cancer. 2018

25. Smith MR, Klotz L, Persson B-E, et al. Cardiovascular safety of degarelix: results from a 12-month, comparative, randomized, open label, parallel group phase III trial in patients with prostate cancer. *The Journal of urology* 2010;184(6):2313-19.

26. Margel D, Peer A, Ber Y, et al. Cardiovascular morbidity in a randomized trial comparing GnRH agonist and GnRH antagonist among patients with advanced prostate cancer and preexisting cardiovascular disease. *The Journal of Urology* 2019;202(6):1199-208.

27. Myovant Sciences dof. Feasibility Assessment and Indirect Treatment Comparison of Therapies for Hormone-Sensitive Advanced Prostate Cancer, 2022.

28. Myovant Sciences dof. Network Meta Analysis (NMA) of Therapies for Hormone-Sensitive Advanced Prostate Cancer, 2023.

29. Melloni C, Slovin SF, Blemings A, et al. Cardiovascular Safety of Degarelix Versus Leuprolide for Advanced Prostate Cancer: The PRONOUNCE Trial Study Design. *JACC CardioOncol* 2020;2(1):70-81. doi: 10.1016/j.jaccao.2020.01.004 [published Online First: 20200317]

30. Freedland SJ, De Giorgi U, Gleave M, et al. A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk non-metastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design. *BMJ open* 2021;11(8):e046588. doi: 10.1136/bmjopen-2020-046588 [published Online First: 20210812]

31. Lopes RD, Higano CS, Slovin SF, et al. Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Prostate Cancer: The Primary Results of the PRONOUNCE

Randomized Trial. *Circulation* 2021;144(16):1295-307. doi: 10.1161/circulationaha.121.056810 [published Online First: 20210830]

32. ClinicalTrials.gov. A Trial of Degarelix in Patients with Prostate Cancer 2014 [Available from: https://clinicaltrials.gov/ct2/show/results/NCT00946920.

33. Bolla M, Neven A, Maingon P, et al. Short Androgen Suppression and Radiation Dose Escalation in Prostate Cancer: 12-Year Results of EORTC Trial 22991 in Patients With Localized Intermediate-Risk Disease. *Journal of Clinical Oncology* 2021;39(27):3022-33. doi: 10.1200/jco.21.00855

34. Tombal BF, Gomez-Veiga F, Gomez-Ferrer A, et al. A phase 2 randomized open-label study of oral darolutamide monotherapy vs. androgen deprivation therapy in men with hormone-naive prostate cancer (EORTC-GUCG 1532). *Journal of Clinical Oncology* 2023;41(6_suppl):160-60. doi: 10.1200/JCO.2023.41.6_suppl.160

35. Koontz BF, Karrison T, Pisansky TM, et al. NRG-GU011: A phase II double-blinded, placebo-controlled trial of prostate oligometastatic radiotherapy with or without androgen deprivation therapy in oligometastatic prostate cancer (NRG PROMETHEAN). *Journal of Clinical Oncology* 2023;41(6_suppl):TPS283-TPS83. doi: 10.1200/JCO.2023.41.6_suppl.TPS283

36. Myovant Sciences dof. Clinical Study Report , Primary Analysis (HERO), 2020.

37. Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: A 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU International* 2008;102(11):1531-38. doi: http://dx.doi.org/10.1111/j.1464-410X.2008.08183.x

38. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane, 2022.

39. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods* 2020;n/a(n/a) doi: 10.1002/jrsm.1411

40. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of

Randomised Controlled Trials. Last updated 2016 Sheffield: Decision Support Unit, ScHARR, University of Sheffield,, 2011.

41. Cirne F, Aghel N, Petropoulos JA, et al. The Cardiovascular Effects of Gnrh Antagonists in Men with Prostate Cancer. *Eur Heart J Cardiovasc Pharmacother* 2021 doi: 10.1093/ehjcvp/pvab005 [published Online First: 2021/01/21]

42. Uttley L, Whyte S, Gomersall T, et al. Degarelix for Treating Advanced Hormone-Dependent Prostate Cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *Pharmacoeconomics* 2017;35(7):717-26. doi: 10.1007/s40273-016-0481-1 [published Online First: 2016/12/13]

43. Albertsen PC, Klotz L, Tombal B, et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *European Urology* 2014;65(3):565-73.

44. NHS Business Services Authority. Prescription Cost Analysis – England – 2022-23 2023 [updated 27th July 2023. Available from: https://www.nhsbsa.nhs.uk/statistical-collections/prescription-cost-analysis-england/prescription-cost-analysis-england-2022-23.

45. Brady BL, Pruett JA, Winer IH, et al. Prevalence of Major Adverse Cardiac Events (MACE) in Patients with Prostate Cancer (PC) Receiving Androgen Deprivation Therapy (ADT) in the United States. *Data on file Presented at: Virtual ISPOR Europe 2020; November 16–19, 2020* 2020

46. D'Agostino Sr RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117(6):743-53.

47. Nam W, Choi SY, Yoo SJ, et al. Factors associated with testosterone recovery after androgen deprivation therapy in patients with prostate cancer. *Investig Clin Urol* 2018;59(1):18-24. doi: 10.4111/icu.2018.59.1.18 [published Online First: 2018/01/16]

48. Ozyigit G, Hurmuz P, Yuce D, Akyol F. Prognostic significance of castrate testosterone levels for patients with intermediate and high risk prostate cancer. *World J Clin Oncol* 2019;10(8):283-92. doi: 10.5306/wjco.v10.i8.283 [published Online First: 2019/09/19]

49. Nabid A, Marie-Pierre G, Vigneault E, et al. Significance of Testosterone Suppression in Localized Prostate Cancer Treated with Androgen Deprivation Therapy and Radiotherapy:

Data from 2 Phase 3 Trials. *Int N Rad Oncol Bio Phys* 2017;99(1):S131-S32. doi: https://doi.org/10.1016/j.ijrobp.2017.06.307

50. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2019;381(1):13-24. doi: 10.1056/NEJMoa1903307 [published Online First: 2019/06/01]

51. Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2017;377(4):352-60. doi: 10.1056/NEJMoa1704174 [published Online First: 2017/06/06]

52. Institute for Clinical and Economic Review. Antiandrogen therapies for nonmetastatic castration-resistant prostate cancer: effectiveness and value, 2018.

53. Li TT, Shore ND, Mehra M, et al. Impact of subsequent metastases on costs and medical resource use for prostate cancer patients initially diagnosed with localized disease. *Cancer* 2017;123(18):3591-601. doi: 10.1002/cncr.30784 [published Online First: 2017/05/26]

54. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med* 2018;378(15):1408-18. doi: 10.1056/NEJMoa1715546 [published Online First: 2018/02/09]

55. Armstrong AJ, Lin P, Tombal B, et al. Five-year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer from the PREVAIL Trial. *Eur Urol* 2020;78(3):347-57. doi: 10.1016/j.eururo.2020.04.061 [published Online First: 2020/06/13]

56. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med* 2018;378(26):2465-74. doi: 10.1056/NEJMoa1800536 [published Online First: 2018/06/28]

57. Parry MG, Nossiter J, Cowling TE, et al. Toxicity of pelvic lymph node irradiation with intensity modulated radiation therapy for high-risk and locally advanced prostate cancer: a national population-based study using patient-reported outcomes. *International Journal of Radiation Oncology* Biology* Physics* 2020;108(5):1196-203.

58. Hall F, de Freitas HM, Kerr C, et al. Estimating utilities/disutilities for high-risk metastatic hormone-sensitive prostate cancer (mHSPC) and treatment-related adverse events. *Qual*

Life Res 2019;28(5):1191-99. doi: 10.1007/s11136-019-02117-9 [published Online First: 2019/02/16]

59. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *PharmacoEconomics* 2023;41(2):199-207. doi: 10.1007/s40273-022-01218-7

60. Dolan P. Modeling valuations for EuroQol health states. (0025-7079 (Print))

61. National Institute for H, Care E. NICE health technology evaluations: the manual [PMG36] 2022 [Available from: https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation.

62. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. 1999

63. Ara R, Brazier JE. Populating an Economic Model with Health State Utility Values: Moving toward Better Practice. *Value in Health* 2010;13(5):509-18. doi: https://doi.org/10.1111/j.1524-4733.2010.00700.x

64. Parker C, Zhan L, Cislo P, et al. Effect of radium-223 dichloride (Ra-223) on hospitalisation: An analysis from the phase 3 randomised Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial. *Eur J Cancer* 2017;71:1-6. doi: 10.1016/j.ejca.2016.10.020 [published Online First: 2016/12/09]

65. Rana D, Geue C, Baillie K, et al. Healthcare Costs for Metastatic Castration-Resistant Prostate Cancer Patients Treated with Abiraterone or Enzalutamide. *PharmacoEconomics-Open* 2021:1-11.

66. Iqvia. IQVIA dispensing data [data on file], 2023.

67. National Institute for H, Care E. Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA412) 2016 [Available from: https://www.nice.org.uk/guidance/ta412.

68. NHS England. 2021/22 National Cost Collection Data Publication [updated 19 May 2023. Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/2023.

69. Scheme NHSP. [Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.england.nhs.uk%

2Fwp-content%2Fuploads%2F2023%2F03%2F23-25NHSPS_23-24-prices-workbook-pay-award.xlsx&wdOrigin=BROWSELINK.

70. National Institute for H, Care E. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated 2016 [Available from: https://www.nice.org.uk/guidance/ta377.

71. Danese MD, Gleeson M, Kutikova L, et al. Estimating the economic burden of cardiovascular events in patients receiving lipid-modifying therapy in the UK. *BMJ open* 2016;6(8):e011805. doi: 10.1136/bmjopen-2016-011805 [published Online First: 2016/08/09]

72. Xu XM, Vestesson E, Paley L, et al. The economic burden of stroke care in England, Wales and Northern Ireland: Using a national stroke register to estimate and report patient-level health economic outcomes in stroke. *European stroke journal* 2018;3(1):82-91. doi: 10.1177/2396987317746516 [published Online First: 2018/06/15]

73. Service NH. 2019/20 National Cost Collection data Version 2. 2022

74. Addicott R, Dewar S. Improving choice at end of life: a descriptive analysis of the impact and costs of the Marie Curie Delivering Choice Programme in Lincolnshire: King's Fund 2008.

75. Jones K, Burns A. Unit Costs of Health and Social Care 2022. *Unit Costs of Health and Social Care* 2022

76. Georghiou T, Davies S, Davies A, Bardsley M. Understanding patterns of health and social care at the end of life. *London: Nuffield Trust* 2012

8 APPENDICES

Appendix 1 EAG assessment of company's clinical effectiveness systematic literature review methods

Table 44 EAG appraisal of systematic review methods

Systematic review components and processes	ERG response (Yes, No, Unclear)	Comments
Was the review question clearly defined using the PICOD framework or an alternative?	Unclear	The CS refers to a specific research question but does not explicitly define it. A PICOS framework to identify relevant studies is provided (CS Table 68).
Were appropriate sources of literature searched?	Yes	MEDLINE (Ovid); Embase (Ovid) Cochrane CENTRAL and CDSR (Ovid) Relevant grey literature – conferences and websites.
What time period did the searches span and was this appropriate?	Database inception to April 2023	Searches were approx. 9 months out of date when the EAG received the CS. The EAG has not run any update searches for this period.
Were appropriate search terms used and combined correctly?	Yes	Used both subject headings and free text terms. All relevant.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes and yes	Inclusion/exclusion criteria for SLR specified in Appendix D1.1 (CS Table 68). Criteria are broader than decision problem, e.g. eligible interventions include other GnRH/LHRH antagonists and GnRH/LHRH agonists; eligible comparators include any of the above interventions, plus any treatment that facilitates an indirect comparison. Inclusion/exclusion criteria for NMA (CS Appendix D1.1, Table 72). differs from SLR inclusion criteria (CS Table 68). E.g.

		population is adult men with HSPC but does not specify advanced HSPC. E.g. NMA does not include open label extension studies; phase III RCTs eligible but not phase II (except in the absence of a phase III trial for a given intervention vs comparator).
Were study selection criteria applied by two or more reviewers independently?	Yes	Confirmed in company response to clarification question A3
Was data extraction performed by two or more reviewers independently?	Yes	Confirmed in company response to clarification question A3
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	Cochrane Risk of Bias version 2.0. Graphical summary of risk of bias judgements given in Appendix D1.1 Figure 28, plus a brief narrative summary. However, it is not stated which outcome measure was the subject of the RoB appraisal (RoB v2 is outcome specific).
Was risk of bias assessment (or other study assessment) conducted by two or more reviewers independently?	No	Critical appraisal was performed by one reviewer, with a second reviewer checking the appraisal. (Confirmed in response to clarification question A3). EAG has no concerns.
Is sufficient detail on the individual studies presented?	No	Limited baseline characteristic reported in the CS. However further detail was provided in response to clarification question A13 and A14. Fewer details of Study NCT02083185 are presented
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken,	Yes	See section 3.3 and 3.4 of this report for details of the NMA

were appropriate methods used?		
PICOD – population, intervention, comparator(s), outcome(s) and study design(s).		

Appendix 2 EAG critique of economic model

Table 45 EAG summary and critique of key features of the economic model

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
Population			
Base case population and subgroups (LA, BR, mHSPC)	The company base case an advanced HSPC population, comprising: 27% LA, 41% non-metastatic BR, and 32% metastatic HSPC (distribution at baseline in HERO trial). In response to CQ B2, results also reported for separate subgroups (LA, BR and mHSPC).	We agree with the use of a pooled population with a mix of subgroups as in the HERO trial. But results should also be reported for the separate subgroups, given uncertainty over the population mix in clinical practice, and potential differences in cost-effectiveness.	EAG subgroups: report EAG results for LA, BR and mHSPC separately, as well as for the pooled population.
History of MACE	Baseline prevalence of prior MACE 30.4% from Albertson et al. 2014 used, rather than HERO trial population (37.7%). Age adjustment used in the original CS removed in response to CQ B1, as the mean age in the Albertson datset and HERO trial were very similar (71 years).	Not clear which source is more representative of the population in practice. We prefer HERO prevalence (37.7%) as this is consistent with other baseline characteristics and clinical outcome data used in the model.	EAG preferred analysis: 37.7% with prior MACE at baseline (as in the HERO trial population) EAG subgroups: report results for patients with/without prior MACE at baseline (100%/0% prior mace)
Spinal metastases subpopulation	Cost effectiveness of relugolix vs. degarelix in the subpopulation of	There is insufficient data specific to people with spinal metastases in the	KEY ISSUE

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
	patients with spinal metastases is assumed to be the same as in the mHSPC population.	HERO or other trials in the NMA to explore this assumption.	
High-risk localised subpopulation	Cost effectiveness assumed to be generalisable to the high-risk localised adjuvant and neoadjuvant settings, given that the MHRA granted these licence extensions without supplementary trial data, and the rate of MACE is unlikely to differ.	High-risk localised and locally advanced HSPC are generally treated in the same manner. But ICERs may differ due to diferring risks of progression and duration of treatment differs in adjuvant and neoadjuvant settings.	KEY ISSUE
Comparators			
Blended comparator	47% leuprorelin, 33% goserelin, and 20% triptorelin. In response to CQ B3, ICERs also reported vs. least and most expensive GnRH agonists. Model structure limits number of comparators.	Important to report ICER for separate GnRH agonists, given differing prices and uncertainty over the % split of prescribing for the specific prostate cancer indication.	Report against the least and most expensive GnRH agonist drugs alongside results for the company's blended comparator.
Clinical effectiveness and extrapolation			
Effects on testosterone suppression	GnRH agonists are assumed to have equal efficacy based on clinical opinion, NMA results (CS B.2.9) and	We agree with this assumption.	Effects on testosterone suppression

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
	conclusions in NICE appraisal of degarelix (TA404).		
Background risk of MACE events	MACE incidence in HERO may not reflect clinical practice. So probabilities of MACE with leuprorelin were estimated from a US claims database (Brady et al. 2020). Distribution of MACE types as observed in HERO.	Uncertainty over generalisability of Brady data and assumptions used for estimation. Distribution of types of MACE also uncertain due to low numbers of MACE in HERO.	EAG correction to calculation of background risk of MACE Additional scenario analysis to test impact of changes to background risk and distribution of MACE types
Treatment effects on MACE incidence	Base case HR relugolix vs. leuprolide from HERO data (HR 0.38). RRs from NMA for spinal metastases subgroup (HR 0.42 for relugolix, 0.33 for degarelix). MACE incidence assumed equal for GnRH agonists.	Uncertainty due to differences in estimated relative effects from different sources. Reason for differences not clear. Agree with assumed equivalence between GnRH agonists.	EAG scenarios: RR for MACE from company NMA and Cirne et al. 2022 meta-analysis. KEY ISSUE
MACE carry-over period	The carry-over period for raised risk of MACE (6.8 months) with GnRH agonists based on mean time to testosterone recovery (Nam et al. 2018).	Assumptions of carry-over period based on weak evidence.	EAG preferred assumption: no carry-over period for increased MACE risk with GnRH agonists. Explore impact of carry-over in scenario analysis.

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
PSA progression for non-metastatic HSPC (LA/BR subgroups)	Constant risk of PSA progression (4.95% per year from HERO trial data), regardless treatment and castrate status. Company scenario: HR 1.65 (95%CI 1.19 to 2.30) for people with versus those without sustained castration.	We agree with the company's approach. Given the small number of events observed for this outcome in the HERO trial, there is uncertainty over the estimate rate of	Explore impact of changing the rate of PSA progression
PSA progression while not on ADT for non-metastatic HSPC	Assumed HR of 10 applied to PSA progression rate in HSPC 'Off treatment' versus 'On treatment' health states. Based on assumed mean duration of treatment interruptions (2 years)	Considerable uncertainty over the mean duration off treatment	Explore impact of changing HR for off- vs. on-treatment
PSA progression for metastatic HSPC	Weibull distribution fitted to HERO KM (pooled treatment arms).	We agree with use of the Weibull. Projected PSA progression free survival similar to LATITUDE and TITAN placebo arms (ADT only)	Explore impact of alternative distributions (lognormal and generalised gamma)
Metastatic progression for HSCPC	Constant risk assumed, based on SEER/Medicare data (7.1% over 11 years)	Reasonable to use a constant risk, given slow rate of metastatic progression in this population. Some uncertainty over generalisability of US 2000-2011 data	Explore impact of changes to risk

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
Metastatic progression for CRPC	Lognormal distribution fitted to MFS KM curve for placebo arm of the SPARTAN trial, with adjustment for assumed use of ARI in model.	Reasonable approach	Explore impact of alternative distributions (generalised gamma and Weibull)
Mortality for non-metastatic HSPC	Assumed the same as for people of the same age in the general population (other than raised risks of fatal MACE with GnRH agonists)	We agree	None
Mortality for metastatic CRPC	Mortality related to prostate cancer estimated by log-logistic survival distribution fitted to OS KM data from the placebo arm of the PREVAIL trial, adjusted for assumed treatment with ARI or chemotherapy.	Reasonable approach	Explore impact of alternative distributions (lognormal and Weibull)
Overall survival for metastatic HSPC	Estimated by adjusting fitted OS curve for mCRPC (as above), using HR=0.40 based on Hussain et al.	Reasonable approach	Explore impact of changes in HR
Health related quality of life			
Health state utilities	Analysis of EQ-5D-5L data from the HERO trial, mapped to 3L UK values using the NICE recommended Hernandez-Alava algorithm. GEE	Methods are appropriate. We had some uncertainty over The company did not demonstrate the	None

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
	regression used to estimate values for health states. Adjusted to reflect general population utilities for people of the same age.		
Disutility with MACE and other adverse events	Disutilities for non-fatal MACE and other adverse events taken from NICE TA404[7] (nonfatal MACE) and NICE TA712[14]	Reasonable	None
Resource use and costs			
Subsequent treatments	The proportions of patients receiving ARIs and chemotherapies were based on assumptions.	Uncertainty over % use of subsequent treatments for nmCRPC and mCRPC health states. Potential impact on ICERs due to longer survival with relugolix (and degarelix) than with GnRH agonists, due to MACE effects.	Add scenarios to test effect of total subsequent treatment cost – use least/most expensive treatment options (refer to table in 4.2.8.4).

Source: Produced by EAG, with company assumptions and justification based on CS Tables 49 and 54
Abbreviations:

Appendix 3 Cost-effectiveness results from the company and EAG base cases

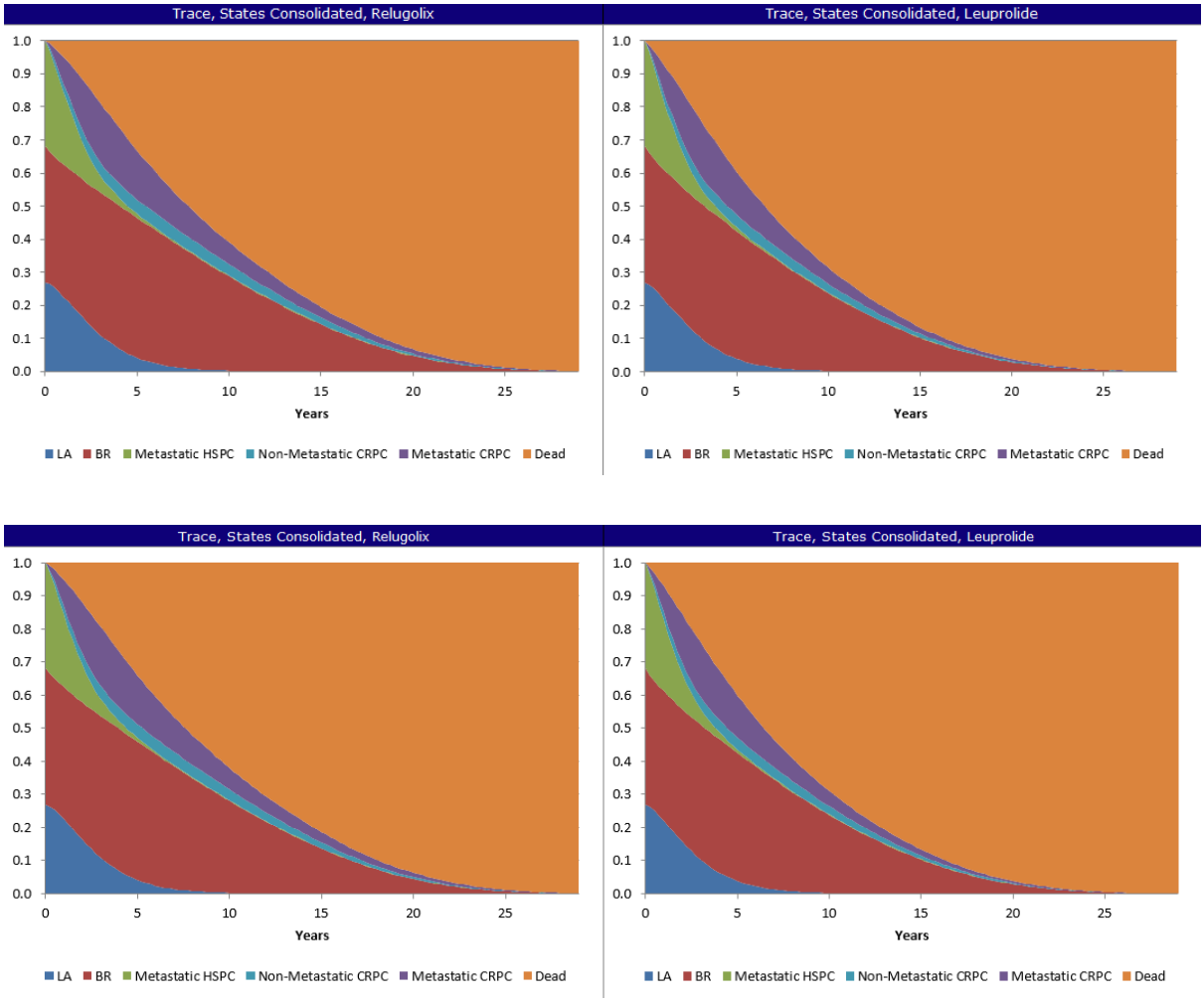


Figure 12 Trace, States consolidated: Company (above) and EAG (below) base cases – Relugolix vs GnRH agonists

Source: economic model – company base case and EAG base case models
LA: locally advanced, BR: biochemical relapse, HSPC: hormone-sensitive prostate cancer, CRPC: castration-resistant prostate cancer, GnRH: gonadotrophin-releasing hormone

Figure 13 Expected discounted QALYs, by comparator and History of MACE (Company and EAG base case)

Source: economic model – company base case and EAG base case models
GnRH: gonadotrophin-releasing hormone, QALY: quality-adjusted life year, MACE: Major cardiovascular events

Figure 14 Expected discounted costs by comparator and History of MACE (Company and EAG base cases)

Source: economic model – company base case and EAG base case models
MACE: Major cardiovascular events, AE: adverse events

Appendix 4 Summary of company scenarios

Table 46 Summary of company's scenarios with MACE parameters coded in the model

Parameter description	Base case	Sc04	Sc 08	Sc 09	Sc 10	Sc 11	Sc 12	Sc 13	Sc 14	Sc 15
Risk of MACE for LHRH agonists	0.094	1			0.200	0.045	0.200	0.045		
Duration carryover MACE	6.8	0								
Relative risk of MACE given prior MACE	2.62	1								
Relative risk of MACE: relugolix	0.38			0.70	0.15			0.15	0.44	
Relative risk of MACE: degarelix	0.38			0.70	0.15			0.15	0.44	
Prior MACE initial probability LA on	0.082		0.023						0.081	0.081
Prior MACE initial probability BR on	0.125		0.036						0.123	0.123
Prior MACE initial probability mHSPC	0.097		0.028						0.096	0.096
No Prior MACE initial state probability LA on tx	0.188		0.247						0.189	0.189
No Prior MACE initial state probability BR on tx	0.285		0.374						0.287	0.287
No Prior MACE initial state probability mHSPC	0.223		0.292						0.224	0.224

Source: Produced by the EAG from the company's economic model
ADT: androgen deprivation therapy, ARI: androgen receptor inhibitors

CONFIDENTIAL

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Addendum 4 to the EAG report: Additional analysis to the relative risk of MACE for comparators post-factual accuracy check

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Date completed	29/04/2024

Confidential information from the company submission is highlighted in blue.

1 Introduction

In this addendum, we performed additional analyses to investigate the sensitivity of the ICER to the relative risk of MACE. We used the EAG preferred assumptions and PAS discount for relugolix to identify threshold values for the relative risk of MACE at which the cost-effectiveness conclusions change, based on £20,000 and £30,000 per QALY decision thresholds. In section 2 we report the threshold analysis for the base case population and in section 3 we show the same threshold analysis focusing on the metastatic HSPC subgroup.

2 Base case population

Table 1**Error! Reference source not found.** details the ICER by relative risk of MACE from 0.95 to 1 (no treatment effect). Figure 1 below shows illustrates this relationship, with relative risk of MACE estimates from references in the company submission and EAG base case and scenarios indicated.

Table 1 Relative risk of MACE with the PAS discount for relugolix

Relative Risk of MACE	ICER (£ per QALY gained)
0.9500	[redacted]
0.9600	[redacted]
0.9761	[redacted]
0.9800	[redacted]
0.9879	[redacted]
0.9900	[redacted]
0.9950	[redacted]
1.0000	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; MACE, major cardiovascular events

We note:

- There is a slow increment in the ICER up to a relative risk of MACE value of 0.9 (see Figure 1). Varying the relative risk from 0.38 (HERO trial estimate and EAG Base case) to 0.9 increases the ICER by £2,287.
- There is asymptotic behaviour above a relative risk MACE value of 0.9 (Figure 1).

- The EAG base case ICER remained below £20,000 per QALY with the relative risk of MACE [redacted] and below £30,000 per QALY gained (remained cost-effective) with the relative risk of MACE [redacted].

3 Subgroup with spinal metastases

We repeated this analysis for the metastatic HSPC subgroup and estimated the net monetary benefits of relugolix versus GnRH agonists and degarelix versus GnRH agonists as a function of the MACE relative risk. We considered willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY, see Figure 2.

- For a WTP of £20,000, the net monetary benefit for Relugolix versus GnRH agonists [redacted] up to the relative risk of MACE [redacted]. Considering a WTP equal to £30,000, the net monetary benefit [redacted].
- For WTP equal to £20,000, the net monetary benefit for Degarelix versus GnRH agonists [redacted] up to the relative risk of MACE [redacted]. Considering a WTP equal to £30,000, the net monetary benefit [redacted].

Figure 1 Threshold analysis for MACE relative risk: EAG preferred analysis with PAS discount for relugolix

ICER (Relugolix vs. GnRH agonists) by relative risk of MACE

Figure 2 Threshold analysis for MACE relative risk: EAG preferred assumptions with PAS discount

Net monetary benefit (Relugolix vs. GnRH agonists and Degarelix vs. GnRH agonists)

Single Technology Appraisal

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5:00pm on Monday 8 April 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Data supporting the license extension/variation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 2 – the statement *"The company believe that the submission can be generalised to support these indications, as the licence extensions were based on the same HERO trial data presented in the CS (which includes a subgroup with high-risk localised HSPC)"* is misleading as it implies that the license variation application was based only on HERO trial data, and that this was the only justification for suggesting that the results could be generalised. The license variation application did use HERO data, as well as phase II data from Study C27003 (as stated on CS page 37). In addition to stating the use of the phase III HERO study as justification for the generalisability of evidence to the full license, Accord also provided the following justification in the CS: 1. ADT as a pharmacological class (without specific mention of individual drugs) is recommended by the latest	Accord believes the statement on page 2 should be reworded as such: *"The company believe that the submission can be generalised to support these indications, as the ADT class (without mention of individual drugs) is recommended and used in routine practice as the mainstay of therapy in all groups in the licensed indication. In addition, the treatment goal remains consistent regardless of subgroup, and evidence to support the use of relugolix according to this treatment goal is available from the phase II C27003 study and the phase III HERO trial in patients across groups of patients according to these definitions."*	The current wording is not a true reflection of the approved marketing authorisation, and also gives the impression that the use of HERO data to support the marketing authorisation is the sole justification for the focus on only part of the license population in the submission.	Descriptions of key issues need to be concise for the benefit of busy decision makers. We have elaborated as follows (italics): "The company believe that the submission can be 2ocalized2d to support these indications, as the licence extensions were based on the same HERO trial data presented in the CS (which includes a subgroup with high-risk 2ocalized HSPC). *It is also noted that ADT as a pharmacological class is recommended by recent clinical guidelines to treat*

NICE, EAU, ESMO, and NCCN treatment guidelines and is used in routine practice as the mainstay of therapy in the aforementioned indications (high-risk localised and locally advanced prostate cancer). Current clinical practice and general perception assumes that there is equivalence amongst drugs in the ADT class. 2. Despite structural and mechanistic differences amongst medications, testosterone suppression constitutes the final common treatment goal whereby all GnRH receptor agonists and antagonists achieve their intended action and is a validated target in all such populations.			*high-risk localised and locally advanced HSPC"*

Issue 2 Inclusion of C27002 in the MACE NMA

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 3 – The EAG states that "*The EAG requested that data from the phase II trial of relugolix versus*	Accord would propose to revise the statement on page 3 as follows: *"The EAG requested that data from the phase II trial of relugolix versus leuprolide (C27002 NCT02083185)*	The current wording implies that Accord had access to the CSR data prior to clarification which they failed to use,	We have revised the text as follows (italics):

leuprolide (C27002 NCT02083185) should be included in the company's NMAs. In response, the company updated their NMA for the outcome of testosterone suppression, but they did not update the NMA for MACE incidence, stating that these data were not available. The EAG notes that the data are available in the clinical study report, which the company has accesss to.". Although the testosterone suppression NMA was updated for the clarification response, this used published data, as the C27002 CSR only became available to Accord after the process to update the NMA had commenced. As later acknowledged in the EAR, Accord are not the originator company, and in order to access the CSR for this study, had made a request for the CSR prior to the original submission, with no success. It was only following receipt of the clarification questions where this was requested by the EAG, that Accord were granted access to the CSR via Myovant from Takeda.	*should be included in the company's NMAs. In response, the company updated their NMA for the outcome of testosterone suppression, but they did not update the NMA for MACE incidence, stating that these data were not available. The EAG notes that the data are available in the clinical study report which was also provided at clarification stage, however it is unclear if this data was available in sufficient time to include in the response.".*	which is misleading. In reality, the timing of the receipt of the CSR and the deadline for submitting the clarification responses was the primary cause of this exclusion. Accord apologises that this was not made clear at the time of response.	"The EAG requested that data from the phase II trial of relugolix versus leuprolide (C27002 NCT02083185) should be included in the company's NMAs. In response, the company updated their NMA for the outcome of testosterone suppression, but they did not update the NMA for MACE incidence, stating that these data were not available. *The EAG notes that the data are available in the clinical study report (CSR), and that the CSR was only obtained by the company itself during the clarification question*

			stage of the appraisal.

Issue 3 Definition of the licensed population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 7-8 – The fourth bullet point in section 2.2.2 currently suggests that the company submission and clarification response refers to "*intermediate-risk localised disease*". The previous 3 bullet points explain that the company submission in fact contained an error and should state the definitions for locally advanced and advanced localised disease, rather than that of intermediate-risk localised disease. As per the clarification response, Accord stated that the text should read *"The definition has been expanded to encompass patients with significant risk of disease progression and/or death, using stage, Gleason grade and PSA level e.g.* • *locally advanced disease (stages T3-T4) and*	We would suggest the following amend to bullet 4 of the list in section 2.2.2. *"Clinical expert advice to the EAG is that the definitions provided by the company in the original CS (in respect to advanced localised disease and CPG stage 2 locally advanced disease) are actually referring to intermediate-risk localised disease instead. However, the company acknowledged this as an error during clarification. Furthermore, the expert commented that high-risk localised disease should be defined as CPG 4 or 5, with high PSA, Gleason score ≥8 and T2 or features of T3 or N1. This was aligned with the company correction during clarification."*	Accord does not believe it is accurate to state that "definitions provided by the company in the CS and their clarification response (in respect to advanced localised disease and CPG stage 2 locally advanced disease) are actually referring to intermediate-risk localised disease instead.)", as any mentions of definitions aligned with intermediate-risk localised disease have been corrected by the company	The last paragraph of company clarification response A1 states: *"However, NICE guidelines use the Cambridge Prognostic Group (CPG) score to risk stratify patients with prostate cancer. Recommendations within the guidelines suggest to "Offer people with CPG 2, 3, 4 and 5 localised or locally advanced prostate cancer 6 months of androgen deprivation therapy before, during or after radical external beam radiotherapy", and "Consider continuing androgen deprivation therapy for up to 3 years for*

• *advanced localised disease (defined as PSA above 20ng/ml and Gleason score ≥ 8).”* The above aligns with clinical advice given to the EAG, as well as NG131 and Moul (2004). Bullet 6 on page 8 also includes information that was corrected at clarification stage with no acknowledgement of the correction. Specifically, the statement *“The company go on to state that “CPG stage 2 locally advanced within the NICE guidelines is aligned with our company submission definition (Gleason score 3 + 4 = 7 (grade group 2) or PSA 10 microgram/litre to 20 microgram/litre and Stages T1–T2).””.* This is not factually accurate, as this was corrected during clarification. In fact, the only mention of intermediate-risk disease (excluding the incorrect inclusion already noted) was on page 42 of the revised CS, which provides the definition of these patients as included in Study C27003. We highlight in the submission that this study includes patients that are outside	Further, the sixth bullet should be amended to reflect the correction that was provided during clarification: *“The company cite NICE clinical guideline 131 (NG131) which recommends to "Offer people with CPG 2, 3, 4 and 5 localised or locally advanced prostate cancer 6 months of androgen deprivation therapy before, during or after radical external beam radiotherapy", and to "Consider continuing androgen deprivation therapy for up to 3 years for people with CPG 4 and 5 localised or locally advanced prostate cancer, and discuss the benefits and risks of this option with them""* And finally, the seventh bullet in the list should be removed, or amended as follows: *“Although the company propose that relugolix should be used in the place of existing ADTs within*	during clarification, or relate to clinical trial inclusion criteria. There is no suggestion in the submission that relugolix should be used in this patient group, other than the acknowledgement that NG131 recommends ADT for people with CPG 2,3,4 and 5 disease. The only other statement made relating to intermediate-risk patients was regarding the inclusion criteria for study C27003. Neither of these inclusions go on to suggest that relugolix should be used in this population.	*people with CPG 4 and 5 localised or locally advanced prostate cancer, and discuss the benefits and risks of this option with them". **CPG stage 2 locally advanced within the NICE guidelines is aligned with our company submission definition (Gleason score 3 + 4 = 7 (grade group 2) or PSA 10 microgram/litre to 20 microgram/litre and Stages T1–T2).”*** The last sentence of this paragraph (highlighted in bold) was discussed with the EAG clinical expert. As stated in the fourth bullet point on page 7 of the EAG report, clinical expert advice was that a Gleason score 3 + 4 = 7 (grade group 2) or PSA 10 microgram/litre to 20 microgram/litre and Stages T1–T2 is not locally advanced disease, but intermediate-risk localised disease. The EAG

of the license, as the majority of patients were within the intermediate-risk group. Further, the HERO trial does not include any patients with intermediate-risk disease (company submission page 51).	*its marketing authorisation, the inclusion of NG131 could suggest that relugolix should be considered for use in the same population as NG131 recommends should receive ADT, which includes intermediate risk localised disease. The EAG notes that GnRH agonists are recommended by NICE in NG131 for intermediate-risk localised disease, which is outside of their licensed indications. Intermediate-risk HSPC patients are not included in the relugolix marketing authorisation (see below section 2.2.3 for details of the label). The company submission also acknowledges that this group of patients falls outside of their license, and are not included in the phase III HERO study, although they are included in the phase II C27003 study. Additional expert clinical advice on this issue may provide further clarification on the definitions relating to advanced prostate cancer."*		therefore stands by its statement on page 7 of the EAG report that "*In the CS and subsequent company clarification response (A1), there is ambiguity as to what the company considers advanced prostate cancer to include."*

Issue 4 Positioning and use of relugolix

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14 – The EAG states in table 3 that they *"interpret information provided in company clarification response A1 implies the company wish relugolix to be considered for patients with intermediate-risk localised disease, which is outside of licensed indications.".* This is not factual, as mentioned above, the clarification response to question A1 stated that the text should read *"The definition has been expanded to encompass patients with significant risk of disease progression and/or death, using stage, Gleason grade and PSA level e.g. locally advanced disease (stages T3-T4) and advanced localised disease (defined as PSA above 20ng/ml and Gleason score ≥ 8).".* This is in line with CPG 4 and CPG5, which is within the definition for the current license.	The statement below should be removed: *"The EAG interpret information provided in company clarification response A1 implies the company wish relugolix to be considered for patients with intermediate-risk localised disease, which is outside of licensed indications."*	This statement is not correct and implies that the company is suggesting use of their product outside of the licensed indications. The initial inclusion of this population has been acknowledged as an error in the submission at clarification stage.	Please see the EAG response to issue 3

Issue 5 Access to CSR / data from Study C27002

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The current wording in the EAR about the availability of MACE data from Study C27002 is not an accurate representation of the situation. On page 21, the EAG notes that *"the clinicaltrials.gov record for this study reports detailed study information including efficacy and safety results (webpage last accessed 20th March 2024). The CS cites the clinicaltrials.gov record"*. Although this is true, it is misleading. None of the clinicaltrials.gov results have been analysed, and in order to include in the indirect treatment comparison,	Accord requests to reword the first two bullets on page 21 as follows: • *"The EAG notes that the clinicaltrials.gov record for this study reports detailed study information including efficacy and safety results (webpage last accessed 20th March 2024). The CS cites the clinicaltrials.gov record. However, these results have not been analysed to inform further analysis in the ITC.* • *The company also mentioned that access to the full trial dataset was "limited" at the time of the submission. The dataset is owned by the trial sponsor, Myovant*	Accord requests that the wording is changed as the current wording suggests that there was no effort to obtain information prior to submission, which goes on to suggest that it "undermines confidence in the SLR specifically and the CS in general". This factual inaccuracy seems to be directly linked to a strong critique of the CS, which could in turn impact the perception of other stakeholders about the CS as a whole.	We disagree with the company regarding the first bullet point on page 21 and we therefore have made no change. The clinicaltrials.gov record for study C27002 reports the number of patients in the trial arms with adverse events, including severe events such as cerebral haemorrage and stroke, which could inform the analysis of MACE. These data, and likewise for other study outcomes, are "analysed" to the extent that event rates and continuous outcomes (means/ medians) are reported per trial am. It is possible to directly use these estimates as inputs to the NMA. Furthermore, it should be possible to make reasonable assumptions for the NMA based on the information in the clinical trial record, and accordingly any suspected bias and uncertainty in the NMA results should be noted.

assumptions about the trial would have to be made that could introduce bias and uncertainty in the results. In the subsequent bullet point on page 21, *"The EAG infer from this that the company had previously made no such request [of access to the CSR for C27002] to the sponsor to inform the preparation of their submission to NICE. If this is the case then it undermines confidence in the SLR specifically and the CS in general."* This inference is not factually accurate, as Accord had requested all CSRs for relugolix studies prior to the deadline for submission, but had not received this ahead of that time, as Myovant were also not	*Sciences (now Sumitomo Pharma Co.) (NB. The original development of relugolix was done by Takeda Pharmaceuticals, and subsequently relugolix was licensed to Myovant Sciences before being licensed by Accord). The company were able to acquire the CSR from the sponsor at the request of the EAG (clarification question A6) stating that this "has been provided to Accord once context regarding the clarification questions was given". However, the company have noted that there was not sufficient time to incorporate the CSR into their clarification response."*		Regarding the second bullet point, we have removed the following sentence: *"The EAG infer from this that the company had previously made no such request [of access to the CSR for C27002] to the sponsor to inform the preparation of their submission to NICE. If this is the case then it undermines confidence in the SLR specifically and the CS in general."*

in possession. As the EAG note in their report, the original development of relugolix was done by Takeda Pharmaceuticals, before being licensed to Myovant Sciences, and subsequently by Accord. Following receipt of the clarification questions, Accord again requested from Myovant the CSRs for the phase II studies, which Myovant were able to acquire at this stage from Takeda. In our clarification response, we state that these were provided “once context regarding the clarifications questions was given”. It is Accord’s assumption that the CSR was able to be obtained at this stage because it had been formally requested as part of the NICE process (rather than by			

an internal series of requests). The same paragraph goes on to say that that *"the company had previously made no such request to the sponsor to inform the preparation of their submission to NICE. If this is the case then it undermines confidence in the SLR specifically and the CS in general."* The first half of this statement is factually inaccurate, which is stated to directly impact on the confidence in the SLR and the CS.			

Issue 6 Reasons for exclusion of Study C27002 from the submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21 – The EAG provides two of the three justifications provided for the	Accord suggests that the EAG reword the section 3.2.1 to discuss reasons	The current section 3.2.1 of the EAR	We disagree with the company that a

exclusion of Study C27002 in the CS. The EAR refers to the lack of information available to Accord at the time of submission (discussed in Issue 5) and the opinion that the company "*does not believe that NCT02083185 provides any additional support for the use of relugolix beyond the evidence given in the HERO trial, since both trials assess relugolix against the same comparator (leuprolide) in the same patient population".* The third justification that has been omitted is that Study C27002 was not statistically powered to assess efficacy outcomes, which was stated explicitly in response to clarification question A9. The EAG also refers to these reasons interchangeably as justifications for the exclusion of C27002 from the CS (sections B2.2 to B2.6), and from the NMA. In response to clarification question A9, Accord lists the reasons for the study's exclusion from the main body of the CS. The first reason has been discussed in detail in Issue 5 of this form and relates to the availability of the CSR during the development of both the CS and the response to	for the exclusion of Study C27002 from sections B2.2 to B2.6, and from the NMA, separate ly. In addition, Accord requests that the EAG includes the explanation that Study C27002 is not powered to detect differences between interventions, which is further justification for its exclusion from the NMA.	conflates inclusion of data into the SLR, NMA, and CS sections B2.2 to B2.6, which is confusing.	trial not statistically powered cannot be included in an NMA (or in meta analysis in general for that matter). Other studies included in the NMA for the MACE outcome were not statistically powered to assess differences between treatments in CV-related events. This applies to the HERO trial which was powered for the primary efficacy outcome but was not powered for safety outcomes. One of the advantages of meta analysis is the additional 'power' gained from combining multiple trials, which can often provide greater

clarification questions. Further, the study was not used to populate the economic model, and as per the NICE user guide *"Sections 2.2 to 2.6 of the submission should include only the trials that were included in the economic model.".* As mentioned above, the third justification provided at clarification stage was that the study has a lack of power to support a statistical comparison between interventions. This is justification for the exclusion from the NMA, rather than from the CS.			precision and certainty in the effect estimates that can be provided analysing each study individually. This is especially important when making indirect comparisons where data are sparse.

Issue 7 Referencing

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 21 – the EAG states that the reference for the *"retrospective real-world evaluation of compliance with relugolix"* (reference 94) is for a different study. The bibliography was updated during clarification at the request of the EAG, but as a result of this, the numbering shifted in the appendices. Accord apologises for the	Provide additional wording to confirm the correct citation: *"a retrospective real-world evaluation of compliance with relugolix (The CS cites a publication in The Oncologist in relation to this study, reference number 94. However, reference 94 in the bibliography is a different study.*	The amendment will enable other stakeholders to refer to the correct citation whilst acknowledging the challenges with referencing experienced	Thank you, we have updated the report accordingly

confusion and can confirm that the study should state reference 90 (Kasparian 2023).	*The EAG has not been able to locate the correct citation for this study, however the company has since confirmed that the citation should refer to 90. Kasparian et al, 2023).”*	during the submission process.	

Issue 8 Errors in table 5 (studies of relugolix)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22 -23 – In table 5, the column indicating inclusion in the CS/SLR is incorrect. As stated, there were some studies included in the CS after exclusion from the SLR, and vice versa. The rows with data for C27002 and C27003 could be misinterpreted, as C27002 states “yes” for inclusion in CS/SLR, whilst C27003 states “no” in the same column. In reality, C27002 was included in the SLR but not in the main CS, whilst C27003 was included in the CS but not in the SLR.	Accord suggests that CS and SLR be presented in separate columns of table 5 to aid comprehension.	The current presentation of data in the table is inaccurate and does not reflect the text that follows.	Table 5 has been updated to separate CS and SLR as suggested.

Issue 9 MACE NMA update

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 54 – *"The EAG believes the exclusion criteria based on study phase to be inappropriate and requested the company to include this study in the NMAs. In company clarification response A11, the company provides an updated NMA for testosterone suppression that includes study C27002 (NCT02083185) but states it was not feasible to include this study in the NMA of MACE as it did not report MACE outcomes. The EAG do not agree as the company are in the possession of the CSR for this study, which reports data on relevant cardiovascular adverse events which occurred during the study. These data could therefore be used to inform the inclusion of the phase II trial in the NMA for MACE. (we*	Accord suggests to reword this section to acknowledge that the NMA could not be updated at the time of clarification, but could be updated subsequently, e.g., Page 54 - *"The EAG believes the exclusion criteria based on study phase to be inappropriate and requested the company to include this study in the NMAs. In company clarification response A11, the company provides an updated NMA for testosterone suppression that includes study C27002 (NCT02083185), based on published data, but states it was not feasible to include this study in the NMA of MACE as MACE outcomes were not reported in the public domain. The EAG notes that the company are now in the*	The current wording suggests that the NMA was possible at the time of clarification but was not carried out, whilst in actuality, the CSR was not obtained with sufficient time to facilitate an NMA update for clarification. Accord apologises that this was not made clearer in their original response.	The company's response to A11 does not report all of the information the company claim it did in relation to this issue. All that is said is: "*At the request of the EAG, the NMA for testosterone suppression has been rerun with the data from NCT02083185 included. Since NCT02083185 did not report MACE outcomes, it was not feasible to include it in the NMA of Major CV-related events (MACE).*" We have removed the sentence in our report ("*The EAG do not agree as the company are in the possession of the CSR for this study")* as the company have clarified that timing prevented them from using it for this analysis. However our point in section 4.4, noting that the clinicaltrials.gov record for this study reports incidence of cardiovascular events within the company's definition of MACE and CV

discuss this further in section 3.4.4) " As per Issue 5 of this response, although Accord were able to obtain access to the C27002 CSR in time to provide as data on file (as requested during clarification), they did not have access to the CSR in sufficient time to rerun the NMA with the CSR data. The NMA updates requested by the EAG (for the inclusion of C27002) were done using publicly available data from the available published abstracts, which did not report on MACE. The EAG also notes on page 67 of the EAR that the clinical trial record does include some published results, however the safety outcomes reported measure CV outcomes and not MACE which may further add heterogeneity to an already heterogeneous MACE definition within the included trials.	*possession of the CSR for this study, which reports data on relevant cardiovascular adverse events which occurred during the study. These data could therefore be used to inform the inclusion of the phase II trial in the NMA for MACE. (we discuss this further in section 3.4.4) "* Page 67 – *"The company did not provide an updated NMA for MACE, stating that study C27002 "did not report MACE outcomes" (response to clarification question A11). The EAG considers this to be a factual inaccuracy as the clinicaltrials.gov record for this study (NCT02083185, last accessed 20th March 2024) reports incidence of cardiovascular events within the company's definition of MACE and CV related events (CS Table 77). These include non-fatal myocardial infarction, non-fatal stroke,*		related events, still stands. For example, it gives CV-related events including non-fatal myocardial infarction, non-fatal stroke. Additionally we note that the results in the clinicaltrials.gov record were included in a published meta-analysis of cardiovascular effects of GnRH antagonists. (Filipe Cirne, Nazanin Aghel, Jo-Anne Petropoulos, Laurence Klotz, Daniel J Lenihan, Fred Saad, Jehonathan Pinthus, Darryl P Leong, The cardiovascular effects of gonadotropin-releasing hormone antagonists in men with prostate cancer, European Heart Journal - Cardiovascular Pharmacotherapy, Volume 8, Issue 3, May 2022, Pages 253–262, https://doi.org/10.1093/ehjcvp/pvab005; specifically see Table 1, figure 2 and figure 3 of this publication) The only change we have made to section 3.4.4 therefore is to remove this sentence: "*Furthermore, the company obtained the CSR for study C27002 from the trial sponsor, and this contains*

	and other non-fatal CV events which would need to be assessed for feasibility (e.g. cerebral haemorrhage, cerebrovascular accident, cardiac arrest, acute coronary syndrome). Some of these measures had low or zero events but nonetheless this isn't reported in the CS or the company's response to clarification question A11. Furthermore, the company has since obtained the CSR for study C27002 from the trial sponsor, and this contains relevant MACE data which they could have used. The EAG considers the NMA of MACE to be incomplete due to omission of this study."		*relevant MACE data which they could have used"*

Issue 10 Risk of bias assessment of HERO study

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 28 – the EAG state *"Contradictorily, the randomisation was flagged as having 'some concerns' (CS Figure 28) in the Cochrane risk of bias assessment, due to insufficient available details about the randomization process. This is inconsistent with the company's own judgement (plus that of the EAG) based on the CRD criteria."* The discrepancy can be explained by the fact that the Cochrane risk of bias assessment is based on published materials (e.g. journals and abstracts, which did not include information on randomisation) rather than the company CSR. This can be observed in the SLR RoB assessment spreadsheet that was provided to the EAG in response to clarification question A4, which states the source of information as well as notes on the assessment.	Accord suggests rewording similar to the below: "The EAG notes that the HERO trial underwent a second critical appraisal based on the Cochrane Risk of Bias tool version 2, as part of a feasibility exercise for the NMA (see section **Error! Reference source not found.**). Contradictorily, the randomisation was flagged as having 'some concerns' (CS Figure 28) in the Cochrane risk of bias assessment, due to insufficient available details about the randomization process. This is inconsistent with the company's own judgement (plus that of the EAG) based on the CRD criteria. However, this can be explained by the fact that the risk of bias assessment was based on publicly available sources, rather than the company CSR."	The discrepancy noted by the EAG can be explained by evidence provided to the EAG during clarification.	Our statement is not a factual inaccuracy, no change made. We would also like to point out that it is not sufficiently clear in the company's response to clarification question A4 that the Cochrane risk of bias assessment was based on published study materials but not also based on the CSR. Likewise, it is not stated in the CS that the CRD critical appraisal was not based on information in the CSR.

Issue 11 NMA reports

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 52 – The EAG states *"In response to clarification questions A10 to A14, the company supplied two NMA feasibility reports, one dated 2022 and the other 2023.* [27 28]*".* Although both relating to the NMA, these reports should be referred to separately, as they constitute distinct reports. The report dated 2022 is referred to as the NMA feasibility assessment, whilst the report data 2023 is the NMA report. The former was written prior to the NMA being conducted, and the objective was to explore the feasibility of conducting an indirect treatment comparison directly following the first update of the SLR. The latter is the report that contains the actual results of the NMA following its completion. Although the information regarding these reports is factual, the labelling and therefore the assumed objective of each of these reports is misleading.	Accord suggests that the EAG should refer to the two reports as per the file names provided to them throughout the EAR: Report dated 2022 = "NMA feasibility assessment report" Report dated 2023 = "NMA report"	The current labelling of these reports is misleading and does not appropriately reflect the content.	The EAG note that both NMA related reports contain a feasibility assessment, as i) the eligibility criteria differ between reports with respect to the inclusion/exclusion of Phase II RCTs if a Phase III RCT that evaluated the same intervention and comparator(s) was included, and ii) some of the outcomes assessed as feasible differ between the two reports. However, the EAG has amended the names of the two reports as

The discrepancy between the numbers in these reports was responded to separately at clarification stage.			the company suggest.

Issue 12 Identification of discrepancies in CS and NMA feasibility assessment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53 – The EAR states *"The EAG identified two studies (EMBARK and PRONOUNCE),[29 30] which were included in CS NMA feasibility report 2022 but do not appear as included studies in CS Appendix D.1.1. Table 69. The EAG has checked publications for both studies and neither study would meet the inclusion criteria for the current SLR.[29-31]".* However, this discrepancy was flagged by Accord during clarification stage when this document was provided.	The statement should be reworded to: *"The EAG was notified of two studies (EMBARK and PRONOUNCE),[29 30] which were included in CS NMA feasibility report 2022 but do not appear as included studies in CS Appendix D.1.1. Table 69. The EAG has checked publications for both studies and neither study would meet the inclusion criteria for the current SLR.[29-31]"*	The current wording in the EAR does not reflect the process to date.	The EAG acknowledges that company clarification response A15 states there are two discrepancies between the SLR inclusions in the submission and the feasibility report. One of these was PRONOUNCE and the other NCT00946920. The EAG has performed a keyword search for "EMBARK", and the associated clinicaltrials.gov record number

			(NCT02319837), and cannot locate either in the company clarification response document. The EAG has therefore amended the wording in the EAG report in relation to PRONOUNCE only.

Issue 13 Feasibility of including NCT00946920

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53 – the EAG states *"NCT00946920,32 which compares degarelix to Goserelin, was not included in the feasibility report as it did not have a comparable outcome in relation to testosterone suppression. On examining the clinical trial record for this study, the EAG does not necessarily consider this statement to be correct. The primary outcome is the cumulative probability of testosterone at castrate level (≤0.5*	Accord suggests to reword to: *"NCT00946920,[32] which compares degarelix to goserelin, was not included in the feasibility report as the company stated that "the observed outcome of NCT00946920 was the proportion of testosterone suppression relative to the administration of degarelix measure as a cumulative probability curve*	The current wording does not acknowledge the difficulty in the methodology of synthesising the evidence for this trial with the available data for other trials.	For the HERO study, multiplying the number of patients in each arm by the percentages who achieved and maintained testosterone suppression below castrate level shown in CSR Table 21,

ng/mL) defined as the proportion of patients with testosterone suppression ≤0.5 ng/mL from Day 28 to Day 364." It was explained during clarification questions, in response to A15, that the observed outcome of NCT00946920 was *"the proportion of testosterone suppression relative to the administration of degarelix measure as a cumulative probability curve (time to event), which is fundamentally different to the other trials in the NMA, which measure TS as the percentage of patients with TS (providing a single percentage value). It was not possible to extract a percentage value from NCT00946920 as the percentage for degarelix would have to be assumed, and reducing time to event curves would remove too much information, enough that it would not be comparable to HERO or other trials measuring TS as a percentage value".* To elaborate, HERO (and others in TS NMA) measure TS as the percentage of patients with TS. This gives a single	*(time to event), which is fundamentally different to the other trials in the NMA, which measure TS as the percentage of patients with TS (providing a single percentage value)." The company also stated that "reducing time to event curves would remove too much information, enough that it would not be comparable to HERO or other trials measuring TS as a percentage value".* *On examining the clinical trial record for this study, the EAG does not necessarily consider this statement to be correct. The primary outcome is the cumulative probability of testosterone at castrate level (≤0.5 ng/mL) defined as the proportion of patients with testosterone suppression ≤0.5 ng/mL from Day 28 to Day 364."*		and rounding to nearest whole number, gives the number of patients in each arm with testosterone suppression to castrate levels (<50ng/dL) (i.e. 0.967 * 622 = 601.474 = 601 and 308*0.888 = 273.504 = 274) that are shown in company clarification response A11 Table 1. The EAG believe that in the same manner, using the results for primary outcome 2 in the NCT00946920 clinicatrial.gov record, the number of patients who achieved testosterone suppression to castrate levels can

percentage value reflecting the proportion of patients with TS. NCT00946920 measures TS as a cumulative probability curve (time to event) comparing degarelix vs Goserelin over time. This shows the probability of TS at each timepoint for degarelix vs Goserelin. NCT00946920 measures testosterone suppression (TS) in fundamentally different ways. Compared to the other TS trials in the NMA, it does not show an overall percentage of TS. This trial shows that the cumulative probability curves show TS rates changing over time instead of an aggregated percentage. To compare them, a percentage value from NCT00946920 would need to be extracted: one for degarelix and one for Goserelin. These would need to be averaged to get an overall percentage. There are noted issues with this: • The percentage for degarelix would have to be assumed. • Reducing time to event curves would remove too much			be calculated for NCT00946920 (i.e. 0.85*565 = 480 and 0.053*282 = 15)

information, enough that it would not be comparable to HERO or other trials measuring TS as a percentage value.			

Issue 14 Identification of Margel 2019

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 54 of the EAR report acknowledges issues relating to the identification of Margel 2019 (which was included in the MACE NMA – *"• Of the three studies included in the NMA for MACE, the study of degarelix versus non-specific GnRH agonist treatment by Margel et al (2019)[26] was "omitted from the search due to an indexing error but would have met eligibility criteria for the NMA" (CS section B.2.10.2.2). This became apparent after the SLR had completed, though it is not stated how the company became aware of the study. The CS does not describe the indexing error and whether this was an error in the company's search strategy or an error in the indexing of references in the source database searched. Neither is there any mention of whether the error was corrected and the search repeated to identify any other eligible studies which may have been omitted . The upshot of this is that*	Accord proposes that the explanation provided in this response should be incorporated, as the current wording pulls into question the validity of the evidence base supporting the NMAs.	Given that the current wording questions the validity of the evidence base, the company feels it should have been given the chance to comment prior to these conclusions being made, as they could influence the committee's interpretation of the evidence based on false assumptions of the type of "indexing error" that is referred to.	We thank the company for explaining the indexing error, but our report is not factually incorrect based upon the information given in the CS. In the absence of further information it was entirely reasonable to outline the potential negative consequences for the SLR.

it is uncertain whether other eligible studies could have been included, and what impact these would have on the results of the NMA." Although the first half of this point is accurate, Accord feels that the comment around whether other eligible studies were excluded is misleading, as it infers that the error was an issue in the SLR strategy. This was not questioned during clarification stage, and so Accord have been unable to elaborate on why this record was excluded. The "indexing error" that is referred to is an error in the database records which is unrelated to the search strategy. We describe this error below for completeness. On Embase, the first record of this study on the searched databases was created on 28th May 2020, which would not have been captured in the original SLR search executed on 30th March 2020. However, when the first SLR update was run with a start date of 1st February 2020, but as the paper was published in 2019 (and not added to Embase until almost a full year after publication), it was not captured in the search, as only records relating to buserelin were included, if they were published prior to the start date of the SLR update. The methodology allowed for 2 months of overlap, in order to capture any articles not indexed when the previous SLR searches were conducted. However, the 11+ month delay between the first publication (12th June 2019) and its addition to Embase (28th May 2020) meant that the record was not identified via Embase. If Margel 2019 had			Regarding why this was not raised during the clarification stage, this is because there is limited time during the first 10 days of receiving the company submission to identify all the issues where clarification is needed. Inevitably some issues become more apparent over time as our familiarity with the evidence grows and our critque develops. This is one such example.

been indexed on Embase at the same time as MEDLINE (see below), the search strategy and filters would have meant it was included. On MEDLINE, the first record of this study was created on 13th June 2019 (the day after its electronic publication). However, the study was not caught by the search filters, as the key terms listed under this MEDLINE record were GnRH "Agonists" or "Antagonists & Inhibitors" whereas our search filter was designed to capture studies tagged with "relugolix", "degarelix", "hoserelin", "histrelin", "leuprolide", or "triptorelin". In a closer review of this paper, only "degarelix" was mentioned and this is first introduced in the body of the paper and not mentioned in the title, abstract, or keyword sections. It is standard practice to run searches in both databases to capture any inconsistencies in the search filters. However, in this case, there was an issue outside of the company's control that resulted in an unusual omission. During development of the NICE dossier and the second SLR update (conducted in 2023), the team became aware of Margel 2019 through targeted literature searching, and after discovering this "indexing error" that had prevented its identification, it was added to the evidence base due to the applicability to the decision problem and proposed economic case. On page 68 of the EAR, the EAG again state "*The company do not report whether this [indexing] error could*			

have affected other eligible studies. It is therefore uncertain whether other eligible studies could have been included, and what impact these would have on the results of the NMA." As explained above, this was not flagged as an error of concern by the EAG at clarification stage, otherwise the company would have elaborated on the issue in order to alleviate concerns about any records that may have been missed.			

Issue 15 Incomplete sentence / point in the EAR

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 76 – There is an incomplete sentence on this page that states *"In the base case, the probabilities of PSA progression, metastatic progression and overall survival do not differ between 'Castrate' and 'Not Castrate' health states. In addition, utilities "*	Complete the sentence to allow review of the point.	Accord is not able to comment on the factual accuracy of the incomplete point.	Thank you for noting this omission. We have completed this sentence in our report: "*In addition, utilities do are not assumed to differ by castrate status.*"

Issue 16 Redundant cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 80 – *"Baseline characteristics for the spinal metastases subgroup are assumed to be the same as for the broader metastatic HSPC subgroup (**Error! Reference source not found.**)."*	Remove reference to Table 21 as this table does not show the baseline characteristics.	The distribution of the model cohort between subgroups (as depicted in Table 21) is not relevant when assessing the spinal metastases subgroup.	Thank you for highlighting this error. We have deleted the reference to Table 21.

Issue 17 Factual inaccuracies relating to use of the Prescription Cost Analysis data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 81 – Clarification of the relevant indication that may impact the weighting of the treatments in the blended comparator: *"For their base case analysis, the company use a 'blended comparator' of the three GnRH agonists: 47% leuprorelin, 33% goserelin and 20% triptorelin based on Prescription Cost Analysis data for England (CS B.3.5.1.3).44 We note that Prescription Cost Analysis data is not*	Removal of uterine fibroids from list of potential indications.	Although some of the treatments are indicated for uterine fibroids, their use as a 3.75 mg formulation excluded them from the Prescription Cost Analysis data calculations – this analysis only looked at the prescribing of the 11.75 mg or 10.8 mg formulations. Therefore, it is unlikely that this indication	Thank you for highlighting this error. As suggested, we have removed the reference to uterine fibroids as requested.

specific to the indication and GnRH agonists are prescribed for conditions other than prostate cancer, including endometriosis, uterine fibroids and pre- and peri-menopausal breast cancer. There is therefore uncertainty over the proportions of different GnRH agonist drugs prescribed for the treatment of advanced hormone-senitive prostate cancer." The formulation used for uterine fibroids is 3.75mg. The only other conditions relevant for the formulation utilised in the model (11.25mg) are Endometriosis and breast cancer.		impacts the weightings used in the model.	

Issue 18 Missing footnote in table 24

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 87 – Table 24 has a missing footnote	Add footnote	N/A	Thank you for noting this error. We have deleted the footnote marker for relugolix.

Issue 19 Inconsistencies in the calculation of the blended treatment comparator costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 102 - *"The cost of the ADT mix is a simple average of the ADT costs (list prices of relugolix, leuprorelin, Goserelin, and triptorelin). The EAG observed a minor discrepancy in the ADT mix cost: the company assumed an ADT mix cost of £197.43 per three-month model cycle in CS.3.5.1.4, and the EAG calculated the ADT average cost of £204.47. ".* The suggested updated cost of the ADT mix appears to have some inconsistencies in its calculation	The true cost of the ADT mix is believed to be closer to £242.55, per model cycle. The value in the model and report should be updated accordingly.	It appears the original calculation conducted by the EAG used the 4 listed treatments (relugolix, leuprorelin, Goserelin, and triptorelin) to calculate the £204.47. However, there are a few potential issues: 1. The list price of relugolix appears to have been used 2. The pack price of relugolix appears to have been used, not the 3-monthly cost (i.e. ~3x pack price) 3. It is not considered appropriate to use relugolix in this mix, given it is currently being assessed It is agreed that the mix of ADTs should include an antagonist. Therefore, the mix of ADT treatments is suggested to be: • Leuprorelin (3-monthly)	We agree with the issues raised by the company. However, degarelix should not be considered in the ADT mix cost as this is only available for the mHSPC subgroup. Therefore, we assumed that the ADT mix costs £229.39 including the average cost of leuprorelin, goserelin, and triptorelin per three-month model cycle. Due to the corrected ADT mix cost, we updated one scenario in Table 42 ("Patients do not receive initial ADT after becoming castrate resistant").

		• Triptorelin (3-monthly) • Goserelin (12-weekly) • Degarelix Analysing the model cycle cost for each of these four treatments results in an average cost of £242.55	

Issue 20 Incorrect reference to metastatic health state

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 102 – *"Therefore, the cost of follow-up for the metastatic health state was updated from £242.45 to £203.81 per month. The cost of follow-up for the metastatic health state remains £251.94 per month. "* £251.94 should be referring to the non-metastatic health states	Update sentence: *"The cost of follow-up for the **non-**metastatic health state remains £251.94 per month."*	Ensure statement is referring to correct patient population	Thank you for highlighting this error. As suggested, we have amended the text on page 102 to address this.

Issue 21 Misinterpretation of DSA results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

Page 104 (section 5.2.1) - Due to difficulties interpreting ICERs that fall in the SW quadrant of the cost-effectiveness plane (e.g. in the case of degarelix in the spinal mets sub-group), the outcome of interest for the DSA is NMB. This was chosen due to its simplified interpretation, especially if varying a parameter results in ICERs switching quadrants. As such, the interpretation of the tornado diagram is incorrect. There are three parameter changes that resulted in a negative NMB at a WTP threshold of £20,000/QALY (i.e. an ICER >£20,000). These include: 1. Health state utility in BR - on tx 2. Health state utility in BR - off tx 3. Health state utility in BR - on castrate tx”	Review and update the text in section 5.2.1 to reflect the use of net monetary benefit (NMB) as the model’s outcome of interest for the deterministic sensitivity analysis (DSA), not ICERs. Proposed amendments include: *“The company’s results indicate that the parameters relating to health state utilities for biochemical relapse were the main drivers for the model, **reducing** the **NMB** to [redacted], **at a WTP threshold of £20,000** per QALY in the **BR on**/off-treatment sub-health states.”* *“Three parameter changes resulted in a negative NMB at a WTP threshold of £20,000/QALY (i.e. an ICER >£20,000). These include:* *1. Health state utility in BR - on tx*	The current interpretation of the DSA is incorrect as it is based on the assumption that the ICER is the outcome of interest, not the NMB.	Thank you for highlighting this discrepancy. We have made the necessary amendments in section 5.2.1 of the EAG report.

	2. Health state utility in BR - off tx *3. Health state utility in BR - on castrate tx"*		

Issue 22 Inclusion of degarelix in the base case

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 110 – Table 38 should not include degarelix in the base case.	Remove degarelix from the "Company's base case" row	This comparator did not form part of the company's base case due to the restriction to a subpopulation.	Thank you for highlighting this discrepancy. We have amended Table 38, removing degarelix from the EAG base case row.

Issue 23 Incorrect ICER reported in table 38

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 110 – Table 38 ICER for "Goserelin (most expensive)" in the "Locally advanced HSPC (LA)" analysis appears to	ICER for Goserelin (most expensive) in the Locally advanced HSPC (LA) subgroup should read £10,434	Inaccuracy of reported results	Thank you for highlighting this error. We have amended the ICER for Goserelin in Table 38.

have been incorrectly copied from the model			

Issue 24 Incorrect results based on incorrect model settings

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 110 – Table 38 “Metastatic (mHSPC)” results are inaccurate. It appears incorrect settings were changed in the model in order to obtain these results	<table><tr><td rowspan="5">Metastatic (mHSPC)</td><td>Relugolix</td><td>[redacted]</td><td>[redacted]</td><td></td></tr><tr><td>GnRH agonists</td><td>[redacted]</td><td>[redacted]</td><td>£9,632</td></tr><tr><td>Triptorelin (cheapest)</td><td>[redacted]</td><td>[redacted]</td><td>£11,226</td></tr><tr><td>Goserelin (most expensive)</td><td>[redacted]</td><td>[redacted]</td><td>£7,989</td></tr><tr><td>Degarelix</td><td>[redacted]</td><td>[redacted]</td><td>£60,626 (SW quadrant)</td></tr></table>	The way the results were obtained appears to be incorrect, as it does not allow for the changing of the RR of MACE for degarelix/relugolix for this sub-group. These values appear to have been obtained by setting “Initial health state probabilities” (Setup_Settings!E61:E63) to 0%/0%/100% (LA/BR/mHSPC) Instead, the user should set “Exploratory analysis of Spinal Metastases” (Setup_Settings!E56) to “Included”.	Thank you for noting this error. We have corrected it, as requested, in Table 38.

Issue 25 Incorrect inclusion of degarelix in the base case

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 116 – Table 43 should not include degarelix in the base case.	Remove degarelix from the "EAG base case" row	This comparator should not form part of the base case.	Thank you for highlighting this discrepancy. We have removed degarelix from the EAG base case in Table 43

Issue 26 Incorrect results based on incorrect model settings

<table>
<tr><th>Description of problem</th><th colspan="5">Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td rowspan="6">Page 116 – Table 43 Metastatic (mHSPC) results are inaccurate.

It appears incorrect settings were changed in the model in order to obtain these results</td><td rowspan="5">Metastatic (mHSPC)</td><td>Relugolix</td><td>[redacted]</td><td>[redacted]</td><td></td><td rowspan="6">The way the results were obtained appears to be incorrect, as it does not allow for the changing of the RR of MACE for degarelix/relugolix for this sub-group.

These values appear to have been obtained by setting "Initial health state probabilities" (Setup_Settings!E61:E63) to 0%/0%/100% (LA/BR/mHSPC)

Instead, the user should set "Exploratory analysis of Spinal Metastases" (Setup_Settings!E56) to "Included".</td><td rowspan="6">Thank you for noting this error. We have made the requested correction.</td></tr>
<tr><td>GnRH agonists</td><td>[redacted]</td><td>[redacted]</td><td>£12,702</td></tr>
<tr><td>Triptorelin (cheapest)</td><td>[redacted]</td><td>[redacted]</td><td>£14,162</td></tr>
<tr><td>Goserelin (most expensive)</td><td>[redacted]</td><td>[redacted]</td><td>£11,198</td></tr>
<tr><td>Degarelix</td><td>[redacted]</td><td>[redacted]</td><td>£58,950 (SW quadrant)</td></tr>
</table>

Issue 27 Copyright statement

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page i - The statement pertaining to retention of copyright by Accord Healthcare omits some relevant tables that report information from the company submission.	Include tables 22, 23, 26, 27, 28, 30, 32, 34, 35, 37 and 38 in second bullet point (Information in parts of EAG report tables)	The current list does not include all relevant tables, only a sample.	Amended as suggested

Issue 28 Page numbers

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
After page 40, all pages have page number 1	Correct page numbers to reflect actual page numbers	To aid comprehension and ability to reference the EAR in future stages of the appraisal. The current issues mean that the issues in this report refer to the page number according to Word's built in function,	This was caused by a technical error in the report template we are using. We have corrected it but have noticed it sometimes reverts to all page numbers as 1.

		rather than the footer page numbers.	

Issue 29 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
There are a number of typographical errors in the EAR, including pages: 3 (“accesss”), 9 (“as also known as”), 22 (“submiitted”), 26 (“infoprms”), 28 (“the analysis it’s what’s known as”), 29 (“non- inferirority”), 33 (“relevent”), 61 (“degarlix” and “criteira “ and “publicaitons”), 65 (“treatmentl“), 69 (“effets “), 81 (“advanced hormone-senitive prostate cancer”), 88 (“081” should read 0.81),	Correct typographical errors throughout	Negligible impact.	This was caused by a technical error in the report template we are using which disabled the spell checker from working. These corrections have been made in the Erratum

98 (“cmpany’s “), 99 (“leuprolerin”), 108 (“The company’s economic model has a scenario module with 15 additional scenarios” – should read 12), 121 (“$” (should be “£”)), 139 (“eligibe”), 140 (“lable” and “hasd”)			

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
P148 - Figure 1 Expected discounted QALYs, by comparator and History of MACE (Company and EAG base case)	Should be marked as CIC	[redacted]	We have highlighted Figure 13 in Appendix 3 as confidential.

		[redacted]	
P148 - Figure 14 Expected discounted costs by comparator and History of MACE (Company and EAG base cases)	Should be marked as CIC	[redacted]	We have highlighted Figure 14 in Appendix 3 as confidential.