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Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Post factual accuracy check ERRATUM

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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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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.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

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

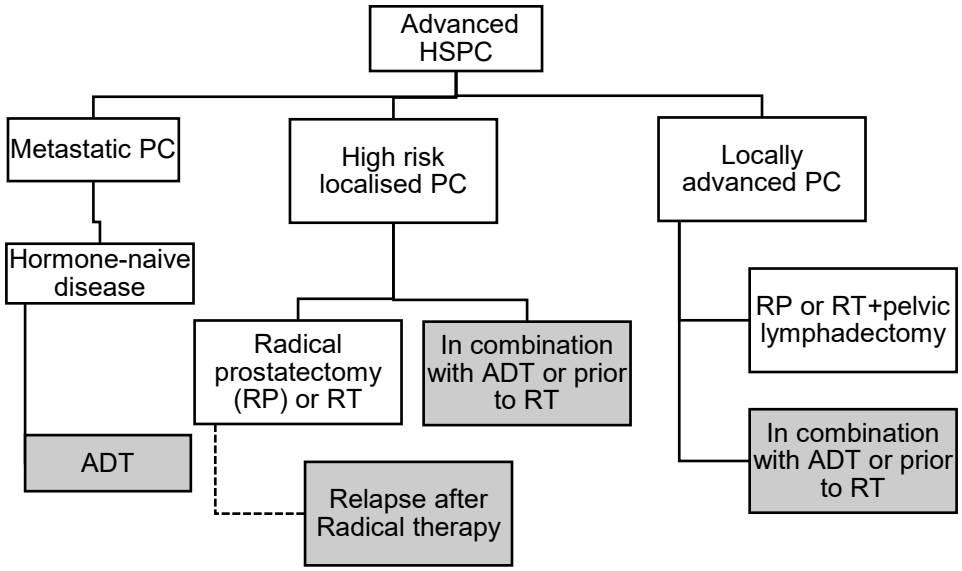
compression and may require treatment with antiandrogens e.g. (e.g., bicalutamide, flutamide, nilutamide);

- 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.

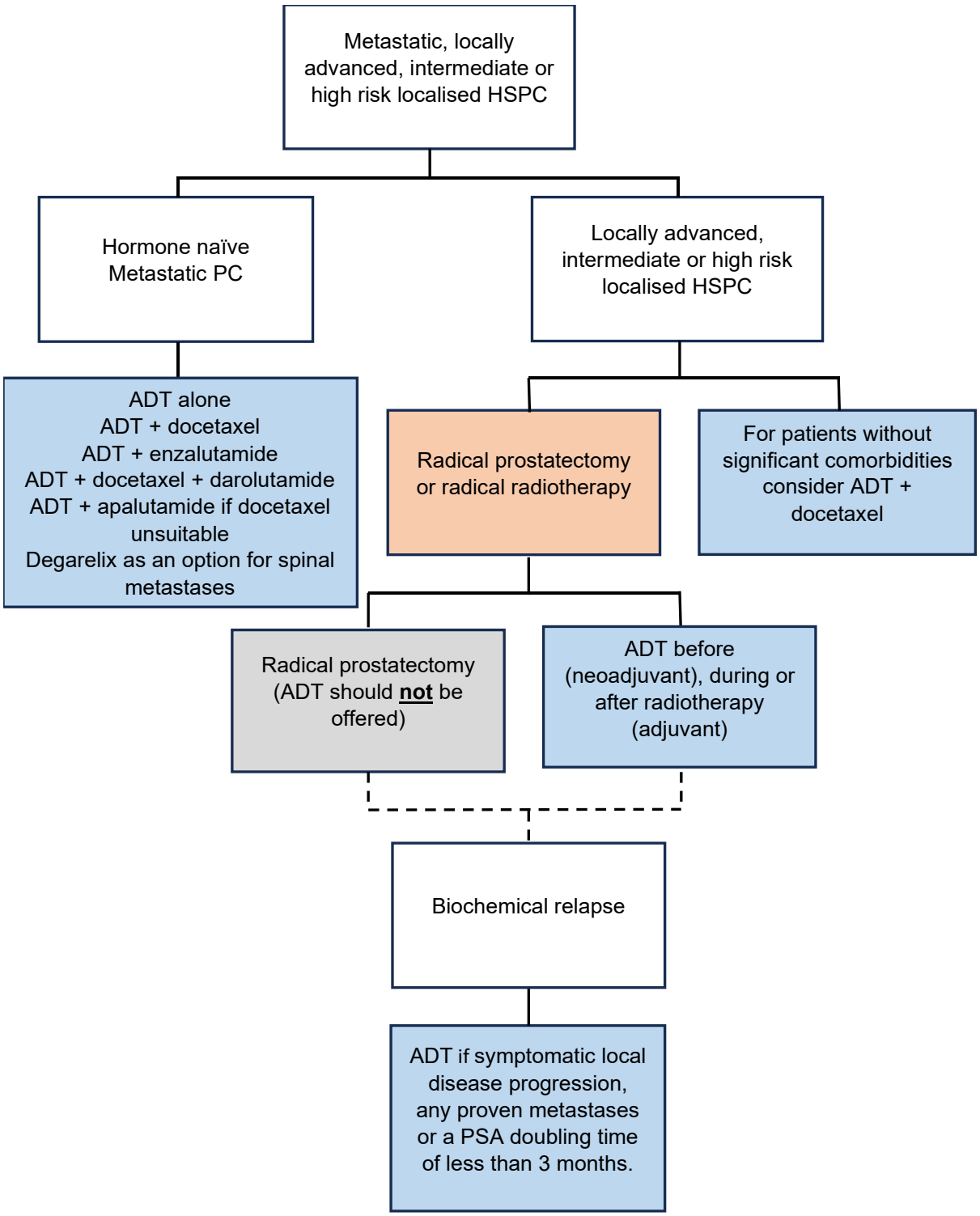


Figure 2 EAG interpretation of the company's position of relugolix in the hormone sensitive prostate cancer care pathway

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.

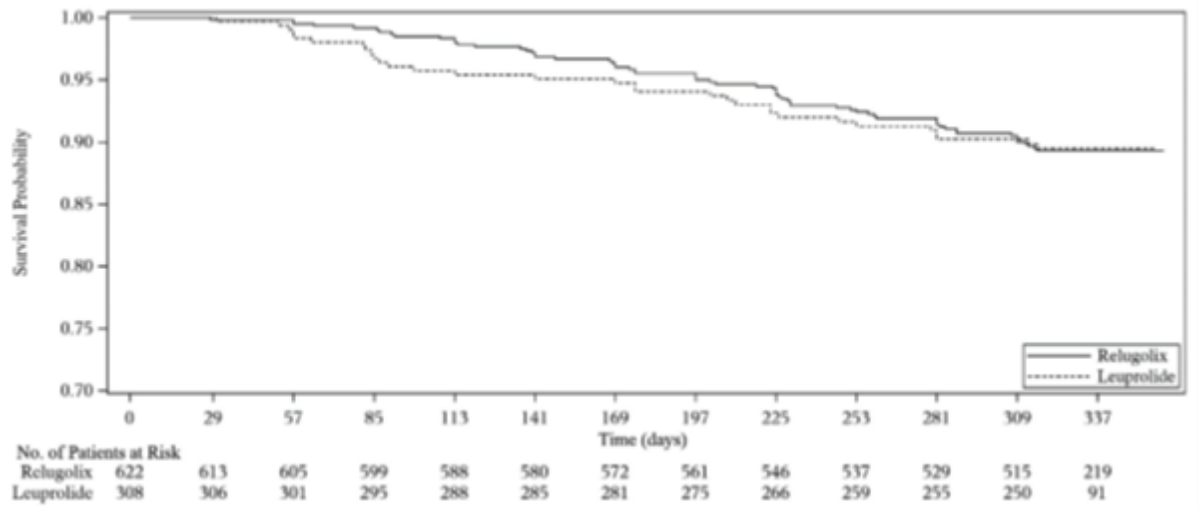


Figure 3 Kaplan-Meier survival curve of time to PSA progression in all patients (modified intention to treat population)

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.

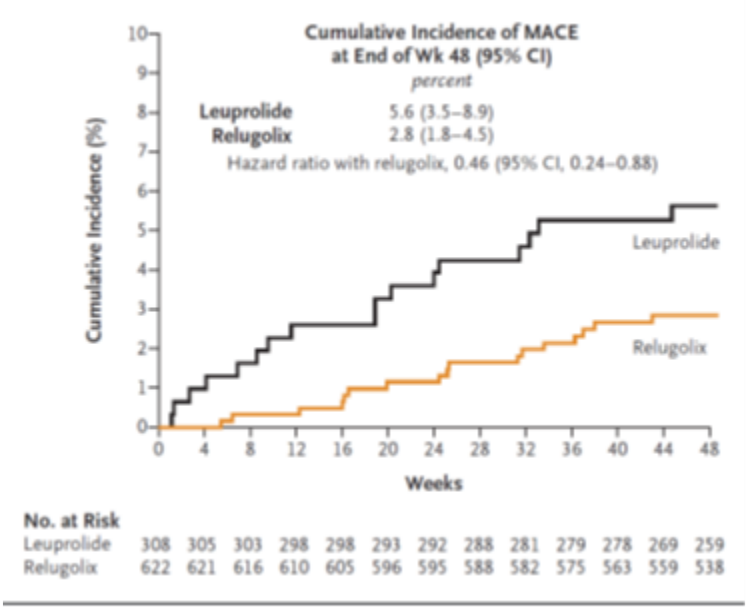


Figure 4 Kaplan–Meier curves showing the cumulative incidence of MACE in the relugolix group and the leuprolide group through 48 weeks of treatment.

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.

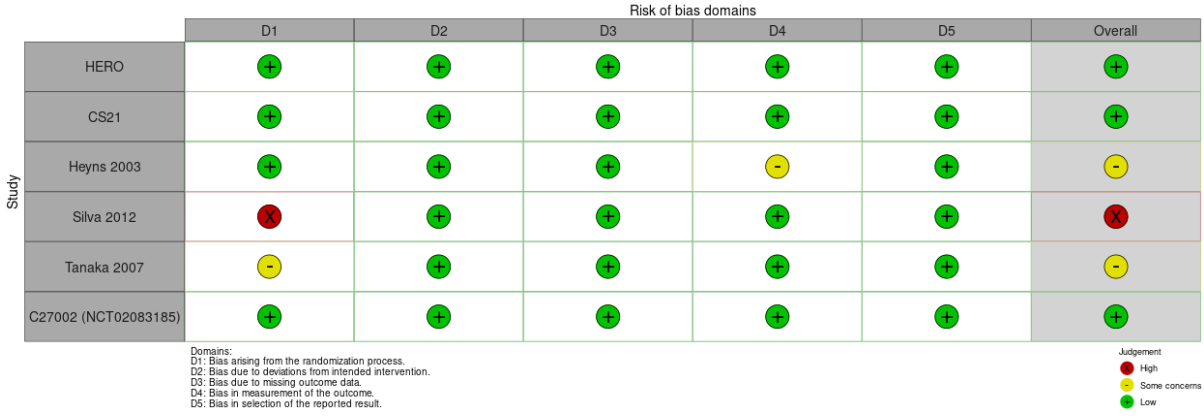


Figure 5 EAG risk of bias assessment for the outcome of testosterone suppression in studies included in the original and updated NMAs of testosterone suppression

Source: Figure created by the EAG using robvis[39]

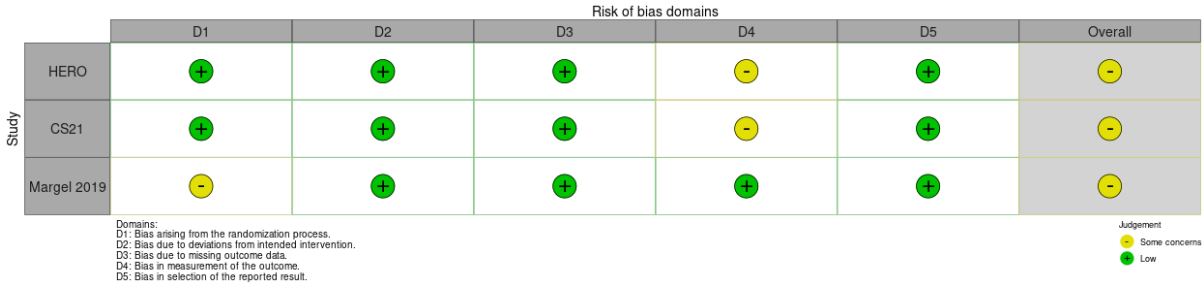


Figure 6 EAG risk of bias assessment for the outcome of MACE in studies included in the NMA of MACE

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).

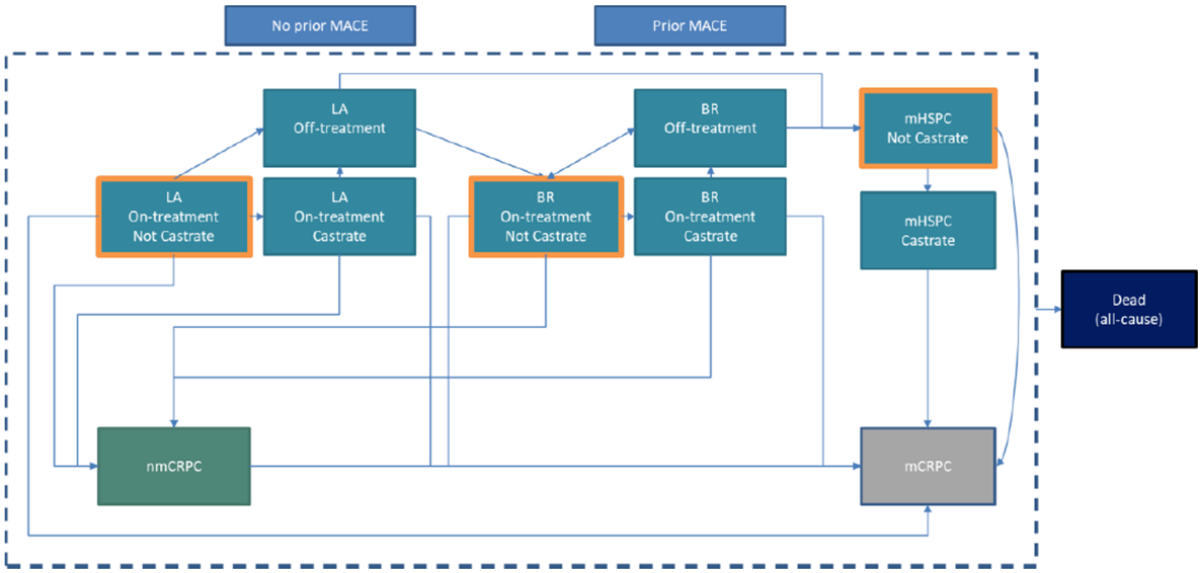


Figure 7 Illustration of economic model structure

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

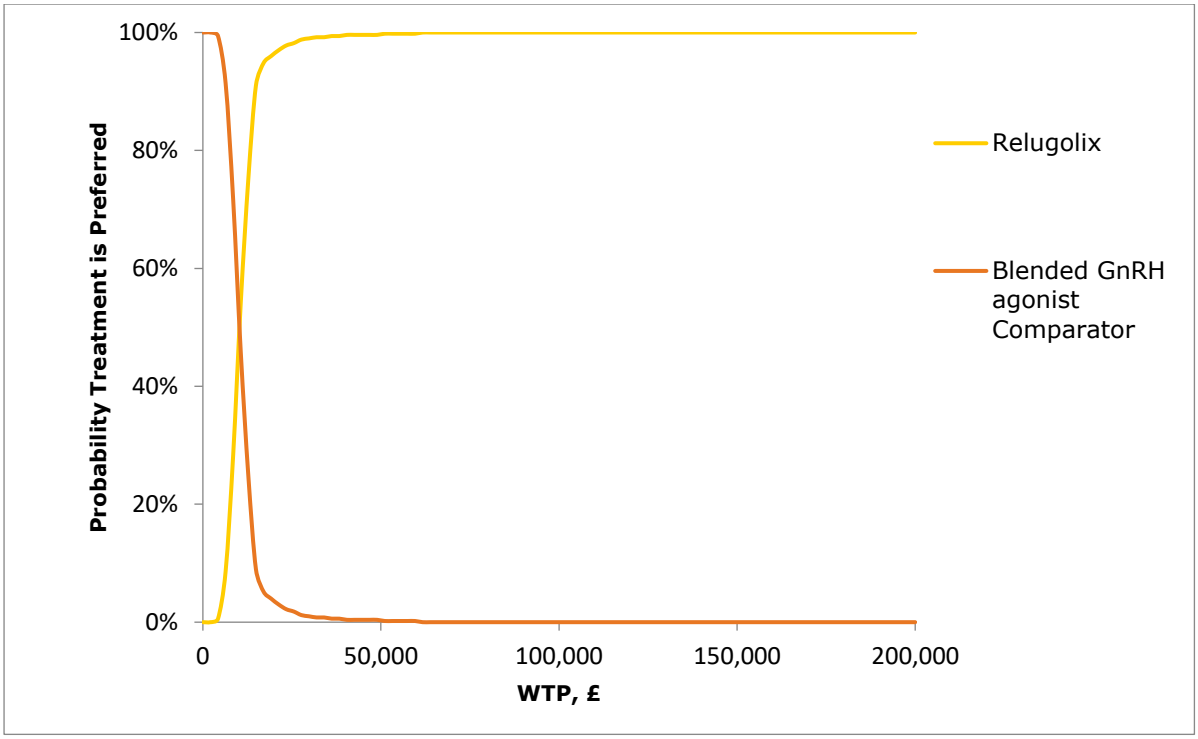


Figure 10 Relugolix cost effectiveness acceptability curve (CEAC)

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.

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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

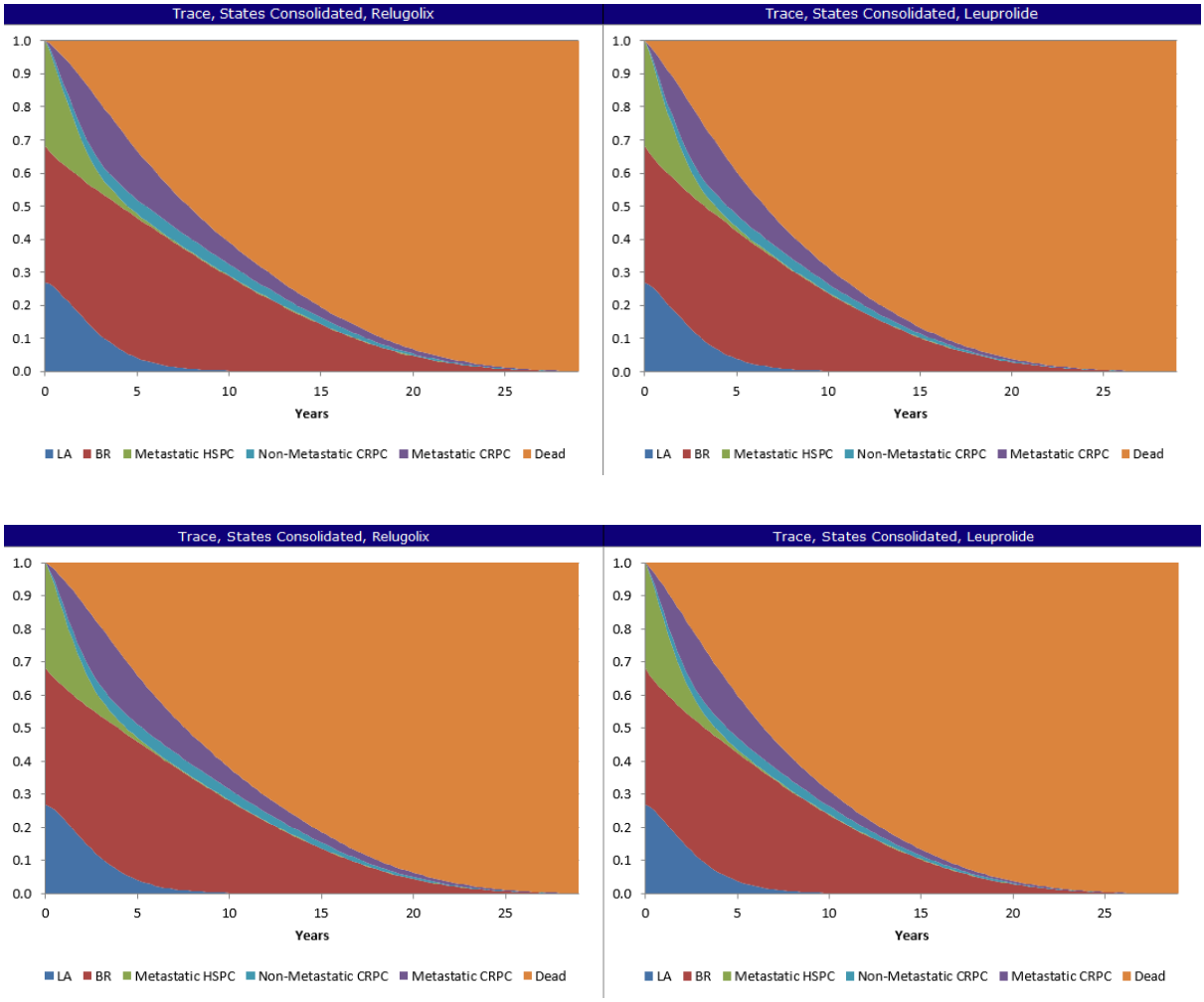

Figure 12 Trace, States consolidated: Company (above) and EAG (below) base cases – Relugolix vs GnRH agonists

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