Health Technology Briefing
August 2022

Relugolix for treating advanced hormone-sensitive prostate cancer

Company/Developer	Accord Healthcare Limited

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 12475	NICE ID: 11787	UKPS ID: 666561

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Relugolix is in clinical development for the treatment of adult males with advanced androgen-sensitive prostate cancer. Prostate cancer develops in the prostate (a small gland which is part of the male reproductive system). When the cancer spreads from the prostate to other parts of the body this is known as advanced prostate cancer. Androgen-sensitive prostate cancer needs androgens (male sex hormones) which are produced in the testis in order for the cancer to grow. Treating hormone-sensitive prostate cancer involves administering medicines which reduce the amount of androgens produced (androgen deprivation treatments) in patients.

Relugolix is a GnRH antagonist which means it blocks the release of GnRH from the brain. The release of GnRH from the brain is a required step in the process that signals the testicles to produce male sex hormones. Through reducing the amount of male sex hormones, relugolix slows down the growth of prostate cancer cells. Unlike other GnRH antagonists, relugolix can be administered as an oral tablet which removes the need for injections. If licensed, relugolix will offer an additional treatment option for adult males with androgen-sensitive advance prostate cancer.

Proposed Indication

Adult males with androgen-sensitive advanced prostate cancer.[1]

Technology

Description

Relugolix (TAK-385, ORGOVYX) is a non-peptide gonadotropin releasing hormone (GnRH) receptor antagonist that competitively binds to GnRH receptors in the anterior pituitary gland preventing native GnRH from binding and signalling the secretion of luteinising hormone and follicle-stimulating hormone. Consequently, the production of testosterone from the testes is reduced.[2] Reducing levels of testosterone in the body is the aim of prostate cancer treatment to supress the growth of prostate cancer cells.[3]

In the phase III clinical trial HERO (NCT03085095), participants received a 120mg tablet of relugolix once daily by oral administration following a loading dose of 360mg (3 x 120mg oral tablets) on day one. Treatment continued for 48 weeks.[1]

Key Innovation

Androgen-deprivation therapy (ADT) is the cornerstone of advanced prostate cancer treatment. ADT can be achieved through surgical castration, or it may be induced either by GnRH agonists or GnRH antagonists. GnRH antagonists, including relugolix, provide a more rapid castration and a safer profile regarding adverse events. Unlike other GnRH antagonists which are administered by injection, relugolix can be administered by oral administration which is easier for patients.[4]

Relugolix leads to rapid inhibition of testicular production of testosterone and its rapid recovery upon discontinuation. In the HERO trial (NCT03085095), relugolix was associated with a superior cardiovascular safety profile compared to GnRH agonists.[5]

Regulatory & Development Status

Relugolix has Marketing Authourisation in the EU for the treatment of adult patients with advanced hormone-sensitive prostate cancer and for the treatment of uterine fibroids.[2]

Relugolix is also in phase II/III clinical development for other indications including:[6]

- Endometriosis related pain
- Heavy menstrual bleeding
- Uterine leiomyoma

Patient Group

Disease Area and Clinical Need

Prostate cancer occurs when abnormal cells start to divide and grow in an uncontrolled manner in the prostate gland.[7] Advanced prostate cancer is where the cancer has spread from the prostate to other parts of the body through the blood stream or the lymphatic system.[8] Initially, prostate cancer requires androgens such as testosterone, or dihydrotestosterone (DHT), for growth and is therefore referred to as androgen dependent, or androgen sensitive, prostate cancer. Androgens exert their effects by binding to androgen receptors which promotes the transcription of androgen-regulated genes that control cellular growth, differentiation and apoptosis.[9,10] Prostate cancer does not normally cause symptoms until the

cancer has grown large enough to put pressure on the urethra. This often results in problems associated with urination including: more urgent and frequent urination, often during the night; difficulty in starting to urinate; straining or taking a long time while urinating; weak flow; feeling that the bladder has not fully emptied.[11] The causes of prostate cancer are largely unknown. However certain risk factors increase the risk of developing the disease: men who are aged 50 or older; men of African-Caribbean descent; men with a first-degree relative who has had prostate cancer.[11]

Amongst males, prostate cancer is the most common cancer in the UK, accounting for 27% of all new male cancer cases (2016-18). The age standardised incidence rate of prostate cancer in England is 186.4 per 100,000 amongst males.[12] In England (2020-21), there were 60,023 finished consultation episodes (FEC) and 55, 799 admissions for malignant neoplasm of the prostate (ICD-10 code C61) which resulted in 39,040 day cases and 58,293 FCE bed days.[13] In England (2017), there were 41,201 patients diagnosed with prostate cancer and 10,146 deaths registered where prostate cancer was the underlying cause.[14] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for prostate cancer were 96.6% and 86.6% respectively.[15]

Recommended Treatment Options

For treatment of hormone-sensitive metastatic prostate cancer the National Institute for Health and Care Excellence (NICE) currently recommends:[16]

- Enzalutamide
- Abiraterone (newly diagnosed, high risk)
- Apalutamide with androgen deprivation therapy

For treatment of advanced hormone-dependent prostate cancer NICE currently recommends degarelix.[17]

Clinical Trial Information

Trial	**HERO**, NCT03085095, 2017-000160-15; A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer **Phase III** – Completed **Locations:** 12 EU countries, UK, US, Canada and other countries **Actual study completion date:** November 2021
Trial Design	Randomised, open-label, parallel group assignment
Population	N=1134; males aged 18 years and older; adenocarcinoma of the prostate; newly diagnosed androgen-sensitive metastatic disease or advanced localised disease unlikely to be cured by local primary intervention with either surgery or radiation with curative intent
Intervention(s)	Relugolix (oral tablet)
Comparator(s)	Leuprolide acetate (subcutaneous injection)
Outcome(s)	Primary outcome measure: Sustained castration rate [Time frame: From week 5, day 1 (day 29) to week 49, day 1 (day 337)]

	See trial record for full list of outcome measures
Results (efficacy)	See trial record
Results (safety)	See trial record

Trial	**NRG PROMETHEAN, NCT05053152;** A phase II double-blinded, placebo-controlled trial of prostate oligometastatic radiotherapy with or without androgen deprivation therapy in oligometastatic prostate cancer **Phase II** – recruiting **Location:** US **Primary completion date:** October 2024
Trial Design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N=269 (planned); males aged 18 years and older; diagnosis of prostate adenocarcinoma; prior curative-intent treatment to the prostate
Intervention(s)	Relugolix (oral administration) Stereotactic body radiation therapy
Comparator(s)	Placebo (oral administration) Stereotactic body radiation therapy
Outcome(s)	Primary outcome measure: Radiological progression-free survival (rPFS) [Time Frame: Time from randomisation to the occurrence of radiological progression detected by conventional imaging or death from any cause, assessed up to 5 years] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Trial	**NCT02083185;** A phase 2, randomised, open-label, parallel group study to evaluate the safety and the efficacy of the oral GnRH antagonist TAK-385, together with a leuprorelin observational cohort in patients with prostate cancer **Phase II** - Completed **Locations:** US and Canada **Actual study completion date:** February 2017
Trial Design	Randomised, parallel assignment, open-label
Population	N=136; males aged 18 years and older; prostate adenocarcinoma
Intervention(s)	Relugolix (oral administration)
Comparator(s)	Leuprorelin (subcutaneous injection)
Outcome(s)	Primary outcome measure:

	Percentage of participants with effective castration rate over 24 weeks [Time Frame: Day 1 of week 5 to day 1 of week 25] See trial record for full list of outcome measures
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The estimated cost is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer (GID-TA10860). Expected May 2023.
- NICE technology appraisal. Apalutamide with androgen deprivation therapy for treating hormone sensitive metastatic prostate cancer (TA741). October 2021.
- NICE technology appraisal. Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (TA721). August 2021
- NICE technology appraisal. Enzalutamide for treating hormone-sensitive metastatic prostate cancer (TA712). July 2021.
- NICE technology appraisal. Degarelix for treating advanced hormone-dependent prostate cancer (TA404). August 2016.
- NICE clinical guideline. Prostate cancer: diagnosis and management (NG131). May 2019 (last updated December 2021)
- NICE quality standard. Prostate cancer (QS91). June 2015 (last updated December 2021)

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a.
- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) in the treatment of Prostate Cancer. 16031/P. July 2016.
- NHS England. Clinical Commissioning Policy: Proton Beam Therapy for Cancer of the Prostate. 16020/P. July 2016.

Other Guidance

- European Society for Medical Oncology (ESMO). Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. June 2020.[18]

Additional Information

References

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