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Health Technology Briefing
July 2023

Vepdegestrant for previously treated locally advanced or metastatic ER+/HER2– breast cancer

Company/Developer	Pfizer Limited (UK) and Arvinas, Inc.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 36353	NICE TSID: Not Available	UKPS ID: 668961

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Vepdegestrant is in development for the treatment of patients with oestrogen receptor-positive (ER+) and human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer, who previously received endocrine-based treatment. A locally advanced breast cancer is a stage 3 breast cancer where the cancer has spread from the breast to lymph nodes close to the breast or to the skin of the breast or to the chest wall. Metastatic breast cancer is breast cancer where the cancer has spread to other parts of the body. ER+ breast cancer is a type of breast cancer that expresses the oestrogen hormone receptors (receptors are proteins within or on body cells). HER2 is a protein expressed in some breast cancer cells. HER2- breast cancers have low or no expression of the HER2 protein. Targeted therapies remain an unmet need in the treatment of ER+/HER2- metastatic breast cancer due to the development of resistance to existing hormonal treatment.

Vepdegestrant is a protein degrader designed to specifically target and degrade oestrogen receptors in ER+/HER2- locally advanced or metastatic breast cancer. Vepdegestrant is to be administered orally, once daily in a 28-day continuous dosing schedule. If licenced, vepdegestrant may provide a new treatment option for patients with previously treated ER+/HER2- locally advanced or metastatic breast cancer, who currently have limited treatment options.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

Treatment of adult patients with ER+/HER2– locally advanced or metastatic breast cancer previously treated with endocrine-based therapy.[1]

Technology

Description

Vepdegestrant (ARV-471) is an investigational, oral proteolysis targeting chimera (PROTAC) protein degrader that targets the oestrogen receptor (ER), a highly validated driver of ER+ breast cancer.[2,3] PROTACs are heterobifunctional molecules consisting of one ligand for binding to a protein of interest (POI) and another to an E3 ubiquitin (E3) ligase, connected via a linker. PROTACs recruit the E3 ligase to the POI and cause proximity-induced ubiquitination and degradation of the POI by the ubiquitin-proteasome system.[4] PROTACs are, therefore, engineered techniques for targeted protein degradation, and they have emerged as a promising approach for targeted therapy in various diseases, particularly in cancers.[5]

Vepdegestrant is currently in clinical development for the treatment of ER+/HER2- metastatic breast cancer. In phase III clinical trial (NCT05654623; VERITAC-2), participants will receive a once-daily oral dose of vepdegestrant for a 28-day continuous dosing schedule.[1]

Key Innovation

More effective and tolerable therapies remain an unmet need for the treatment of locally advanced and metastatic breast cancer.[6] For metastatic ER+/HER2- breast cancer, endocrine-based therapy remains the recommended treatment option.[7] However, patients develop resistance to endocrine therapy.[8] In a study with vepdegestrant for the treatment of ER+/HER2- metastatic breast cancer in heavily pre-treated patients, vepdegestrant demonstrated antitumor activity in CDK4/6 inhibitor-pretreated patients with a clinical benefit rate (CBR) of 40% in 47 evaluable patients. This heavily pre-treated patient group had a median of four prior therapies.[9]

If licenced, vepdegestrant may provide a new treatment option for patients with ER+/HER2- metastatic breast cancer.

Regulatory & Development Status

Vepdegestrant does not currently have Marketing Authorisation in the EU/UK for any indication.

Vepdegestrant is also in phase II/III development as a monotherapy or a combination therapy for the treatment of various other lines of breast cancer.[10]

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Patient Group

Disease Area and Clinical Need

Breast cancer is a cancer that starts in the breast tissue.[11] Age, family history, previous breast lump, hormone replacement therapy and contraceptive pill are some of the risk factors for breast cancer.[12] Breast cancer can be grouped according to types, stages and grades.[13] A locally advanced breast cancer is a stage 3 breast cancer where the cancer has spread from the breast to lymph nodes close to the breast or to the skin of the breast or to the chest wall.[14] A metastatic breast cancer occurs when breast cancer has spread to other parts of the body.[15] HR+ breast cancer is a type of breast cancer that has either the oestrogen hormone receptor (ER+) or the progesterone hormone receptor (PR+) or both.[16] HER2 is a protein that helps breast cancer cells to grow quickly.[17] A HER2-negative (HER2-) breast cancer has zero or low levels of HER2 proteins.[17,18] HER2- breast cancers tend to be less aggressive but they are also less likely to respond to treatments that target the HER2 protein.[17,19] The symptoms of HER2- breast cancer may include; breast lump, breast swelling, breast or nipple pain, and bleeding.[20]

Breast cancer is the most common type of cancer in the UK, accounting for 15% of all new cancer cases (2016-2018), with about 1 in 7 women diagnosed with breast cancer during their lifetime, and in rare cases, men can also be diagnosed with breast cancer.[21,22] The age standardised incidence rate of breast cancer in England is 1.3 and 169.2 per 100,000 amongst males and females, respectively.[23] In England (2021-22) there were 244,374 finished consultant episodes (FCEs) and 240,790 admissions for breast cancer (ICD-10 code C50), which resulted in 218,006 day cases and 60,220 FCE bed days.[24] In England (2017), there were 46,109 patients diagnosed with breast cancer (ICD-10 code C50) and 9,569 deaths registered where breast cancer was the underlying cause.[25] For patients diagnosed between 2013 and 2017, and followed up to 2018, the 1-year and 5-year age-standardised survival rates for stage III (locally advanced) breast cancer were 95.5% and 72.0% respectively, and for stage IV (metastatic) breast cancer were 66.0% and 26.2% respectively..[26] HR+/HER2– breast cancer represents about 70% of all breast cancers.[7]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following therapies for the treatment of previously treated locally advanced or metastatic HR+/HER2- breast cancer.[27]

- Abemaciclib with fulvestrant (TA725)
- Palbociclib with fulvestrant (TA836)
- Ribociclib with fulvestrant (TA687)

Clinical Trial Information

Trial	**VERITAC, NCT05654623;** A Phase 3, Randomized, Open-Label, Multicenter Trial of Vepdegestrant (PF-07850327) vs Fulvestrant in Participants with Estrogen Receptor-Positive, HER2-Negative Advanced Breast Cancer Whose Disease Progressed After Prior Endocrine Based Treatment for Advanced Disease **Phase 3** – Recruiting **Location(s):** 6 EU countries, Australia, Canada, USA and other countries **Primary completion date**: August 2024
Trial Design	Randomised, parallel assignment, open-label, active comparator-controlled

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Population	N=560 (planned); patients with ER+/HER2- loco-regional recurrent or metastatic breast cancer; aged 18 years and older, with one line of CDK4/6 inhibitor therapy in combination with endocrine therapy
Intervention(s)	Oral dose of vepdegestrant: once daily in a 28-day continuous dosing schedule
Comparator(s)	Intramuscular injection of fulvestrant
Outcome(s)	Primary outcome measure: - Progression Free Survival - Time Frame: from randomisation date (every 8 weeks for the first 48 weeks and then every 12 weeks thereafter) to date of first documentation of progression OR death (approximately 2 years). See the trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of vepdegestrant is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Elacestrant for treating HER2-negative, ER-positive, advanced breast cancer after endocrine therapy (GID-TA11263). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Sacituzumab govitecan for treating hormone receptor-positive HER2-negative metastatic breast cancer after 2 or more therapies (GID-TA10919). Expected date of issue to be confirmed
- NICE technology appraisal guidance. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA836). October 2022.
- NICE technology appraisal guidance. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA725). September 2021
- NICE technology appraisal guidance. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA687). March 2021
- NICE technology appraisal guidance. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). December 2016
- NICE quality standard. Breast cancer (QS12). June 2016
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 2017

NHS England (Policy/Commissioning) Guidance

- NHS England's West Midlands Expert Advisory Group for Breast Cancer. Clinical Guidelines for the Management of Breast Cancer. December 2016
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

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- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

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Additional Information

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