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Health Technology Briefing
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Elranatamab monotherapy or with daratumumab for previously treated relapsed or refractory multiple myeloma

Company/Developer	Pfizer Limited

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 33800	NICE ID: Not available	UKPS ID: 666497

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Elranatamab, alone or in combination with daratumumab, is in clinical development for the treatment of relapsed or refractory multiple myeloma (MM). MM is a type of bone marrow cancer that is characterised by an abundance of abnormal immune cells, known as plasma cells, in the bone marrow. In the early stages, MM may not cause any symptoms, however it eventually causes a wide range of problems such as persistent bone pain, tiredness, weakness, shortness of breath, repeated infections, unusual bleeding, and kidney problems. In relapsed or refractory MM (RRMM), the patient has gone into complete or partial remission but then the disease has returned (relapsed) or stopped responding to treatment (refractory). Outcomes for patients with disease progression is poor, therefore there is a need to develop new treatment options for RRMM.

Elranatamab is a bispecific antibody, a type of protein that has been designed to attach to two targets at the same time: a protein on the surface of MM cells, and a protein on T cells (cells of the immune system responsible for destroying abnormal cells). By attaching to the two targets at the same time, elranatamab is expected to activate the T cells to kill to MM cells. Elranatamab and daratumumab are administered through an injection under the skin. If licenced, elranatamab, alone or in combination with daratumumab, will provide an additional treatment option for previously treated RRMM patients.

Proposed Indication

Elranatamab monotherapy or in combination with daratumumab for treatment of patients with relapsed or refractory multiple myeloma (RRMM) who have received previous treatment including lenalidomide and a proteasome inhibitor.[1]

Technology

Description

Elranatamab (Elrexfio, PF-06863135) is a humanized B-cell maturation antigen (BCMA)-CD3-targeted bispecific antibody.[2,3] Bispecific antibodies are a form of cancer immunotherapy that bind to and engage two different targets at once. One arm binds directly to specific antigens on cancer cells and the other arm binds to T-cells, bringing both cell types together.[2] Elranatamab is designed to bind to BCMA, which is highly expressed on the surface of MM cells, and the CD3 receptor found on the surface of T-cells, bridging them together and activating and directing T-cells to induce a cytotoxic T-cells response against myeloma cells.[2,3] The binding affinity of elranatamab for BCMA and CD3 has been engineered to elicit potent T-cell mediated anti-myeloma activity.[2]

Elranatamab as a monotherapy or in combination with daratumumab, is in clinical development for the treatment of patients with RRMM who have received previous treatment including lenalidomide and a proteasome inhibitor. In the phase III clinical trial (MagnetisMM-5, NCT05020236), elranatamab is administered via subcutaneous (SC) injection as a monotherapy or in combination with daratumumab SC injection.[1]

Key Innovation

Despite improvements in patient survival, most cases of multiple myeloma (MM) remain incurable, with most patients receiving four or more different lines of therapy throughout their disease course.[4,5] Patients with RRMM after prior therapy with lenalidomide and a proteasome inhibitor are challenging to treat, and outcomes for patients with disease progression after treatment remains poor, highlighting an unmet need in the RRMM population.[3,6] Therefore, the development of novel therapeutic approaches are needed to improve outcomes for patients.[7]

Elranatamab is administered subcutaneously, which may mitigate the risk of potential adverse events, such as cytokine release syndrome (CRS), compared with intravenous dosing.[2,8] Elranatamab is a bispecific antibody, which are a novel form of cancer immunotherapy.[2] Compared to chimeric antigen receptor (CAR) T-cell therapy, another novel T-cell therapeutic strategy, bispecific antibodies have the advantage of being directly available for use, excluding the need for bridging therapy. Furthermore, the rates of grade 3 or worse CRS or neurotoxicity are generally lower compared with CAR T-cell therapies, and therapy can be discontinued if needed, allowing for the use of bispecific antibody treatments in patients with late-stage disease, and older patients.[8] Therefore, if licensed, elranatamab alone or in combination with daratumumab will offer an additional treatment option for previously treated RRMM.

Regulatory & Development Status

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

Elranatamab has the following regulatory designations/awards:

- An innovation passport by the MHRA[9]
- An EMA orphan drug designation in 2021 for the treatment of MM[10]

- An EMA PRIME status for the treatment of patients with RRMM in March 2021[11,12]
- A Breakthrough Therapy by the US FDA for the treatment of people with RRMM in November 2022[2]
- Accelerated approval by the US FDA for adults with RRMM in August 2023[13]

Patient Group

Disease Area and Clinical Need

MM, also known as myeloma, is a type of bone marrow cancer that develops when there is a change in the DNA of the plasma cells.[5,14] The exact cause of MM is unknown, however it is more common in men, adults over 60, black people, and people with a family history of monoclonal gammopathy of unknown significance or MM. MM damages the bones and affects the production of healthy blood cells, and often affects several areas of the body, such as the spine, skull, pelvis and ribs.[5] RRMM is defined as MM that is non-responsive to therapy or progresses within 60 days of the last line of therapy, or previously treated MM that has progressed after prior therapy and requires new therapy.[15] MM may not cause any symptoms in the early stages, but eventually leads to a wide range of problems including bone pain, bone fractures and spinal cord compression, anaemia, repeated infections, raised calcium levels in the blood, unusual bleeding, thickened blood, and kidney problems.[16] Treatment can often help to control the condition for several years, but most cases of MM can't be cured.[5]

Multiple myeloma is the 19th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-2018).[17] The age standardised incidence rate of MM in England is 12.4 and 7.6 per 100,000 amongst males and females respectively.[18] In England (2022-23) there were 155,822 finished consultant episodes (FCEs) and 150,740 admissions for MM (ICD-10 code C900), which resulted in 142,557 bed days and 99,552 FCE bed days.[19] In England (2017), there were 4,799 patients diagnosed with MM.[20] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 79.9% and 49.0% respectively.[21]

Recommended Treatment Options

NICE guidelines recommend the following treatment options for RRMM after at least two lines of prior therapy:

- Lenalidomide in combination with dexamethasone for people who have received two or more prior therapies.[22]
- Daratumumab monotherapy for adults who have received three prior treatments, including a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last treatment.[23]
- Ixazomib with lenalidomide and dexamethasone for adults who have had two or three lines of therapy.[24]
- Isatuximab plus pomalidomide and dexamethasone for adults who have had three previous lines of therapy including lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last treatment.[25]
- Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent.[26]
- Pomalidomide in combination with low-dose dexamethasone for adults who have received at least three treatments including both lenalidomide and bortezomib.[27]

Clinical Trial Information	
Trial	**MagnetisMM-5; NCT05020236; EudraCT 2021-000044-22**; An Open-Label, 3-Arm, Multicentre, Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Elranatamab (PF-06863135) Monotherapy and Elranatamab + Daratumumab Versus Daratumumab + Pomalidomide + Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma Who Have Received At Least 1 Prior Line of Therapy Including Lenalidomide and a Proteasome Inhibitor **Phase III –** Recruiting **Location(s):** Twelve EU countries, UK, USA and other countries **Primary completion date:** December 2024
Trial Design	Randomised, factorial assignment, single masking (outcomes assessor)
Population	N=854 (estimated); aged 18 years and older; prior diagnosis of MM as defined by International Myeloma Working Group (IMWG) criteria; prior anti-multiple myeloma therapy including treatment with lenalidomide and a proteasome inhibitor.
Intervention(s)	• Part 1 safety lead-in dose escalation: elranatamab (SC) + daratumumab (subcutaneous) • Part 2 randomised arm A: elranatamab (SC) • Part 2 randomised arm B: elranatamab (SC) + daratumumab (SC) • Part 3 randomised arm D: alternative elranatamab dosing (SC) + daratumumab (SC) • Part 3 randomised arm E: elranatamab (SC) + daratumumab (SC)
Comparator(s)	Part 2 randomised arm C: daratumumab (SC) + pomalidomide (oral) + dexamethasone (oral)
Outcome(s)	Primary outcomes: • Part 1 safety lead-in: incidence of dose limiting toxicities [Time frame: First 42 days after first elranatamab dose] • Part 2 randomised: progression free survival per IMWG criteria [Time frame: From date of randomisation to date of progressive disease, discontinuation from the study, death, or censoring, whichever occurs first, assessed up to 51 months] • Part 3: frequency of treatment-emergent adverse events [Time frame: From date of first dose of study intervention through minimum of 90 days after last study intervention administration. Reporting of non-serious adverse events ends at start of new anti-cancer therapy] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	Data from the safety lead-in cohort (part 1) of the elranatamab and daratumumab combination showed that after a median (range) treatment duration of 6.8 (0.1-23.1) weeks, most patients (93%) experienced at least one treatment-emergent adverse event (TEAE); with 46% experiencing grade (G)3/4 TEAEs. The most common (≥20%) all causality TEAEs included CRS (50%; all G1-2), neutropenia (29%; 14% G3, 14% G4), and pyrexia (21%; all G1). No patients experienced

	immune effector cell-associated neurotoxicity syndrome. The majority of CRS events occurred after the first dose of elranatamab and no patients permanently discontinued study treatment due to CRS. The median (range) time to onset of CRS was 2 (1-4) days, resulting in elranatamab dose interruption in 7.1% of patients. No dose-limiting toxicities were observed.[28]

Estimated Cost

The cost of elranatamab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Ciltacabtagene autoleucel for treating relapsed and lenalidomide refractory multiple myeloma after 1 to 3 therapies (TA10905). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. REGN5458 for treating relapsed or refractory multiple myeloma (TA11052). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Teclistamab with daratumumab for treating relapsed or refractory multiple myeloma after 1 or more therapies (TA11162). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Idecabtagene vicleucel for treating relapsed or refractory multiple myeloma after 2 to 4 therapies (TA11075). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments (TA11201). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments (TA11203). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Selinexor with bortezomib and low-dose dexamethasone for treating relapsed refractory multiple myeloma (TA10646). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (review of TA658) (TA10979). Expected date of issue to be confirmed.
- NICE technology appraisal. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA870). February 2023.
- NICE technology appraisal. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA783). April 2022.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies (TA171). June 2019.
- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). January 2016.
- NICE clinical guideline. Myeloma: diagnosis and management (NG35). October 2018.
- NICE clinical guideline. Haematological cancers: improving outcomes (NG47). May 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 2017. 16068/P.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised. 2015. B04/Pa.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.

Other Guidance

- European Society for Medical Oncology (ESMO). Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[29]
- International Myeloma Working Group (IMWG). Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. 2021.[30]
- National Comprehensive Cancer Network (NCCN). Guidelines Insights: Multiple Myeloma, Version 3. 2018.[31]
- British Society of Haematology (BSH). Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. 2017.[32]

Additional Information

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