Health Technology Briefing
September 2024

Mezigdomide with dexamethasone and carfilzomib for treating relapsed or refractory multiple myeloma

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 29422	NICE ID: Not Available	UKPS ID: 663521

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Mezigdomide is in clinical development for the treatment of relapsed or refractory multiple myeloma (RRMM) in combination with carfilzomib and dexamethasone after 1 or more prior treatments. Multiple myeloma is a type of blood cancer that is characterised by an abundance of abnormal immune cells, known as plasma cells, in the bone marrow. Symptoms include persistent bone pain, raised calcium levels in the blood, unusual bleeding and kidney problems. RRMM can be defined as multiple myeloma that is non-responsive to therapy, disease that progresses within 60 days of the last administration of therapy, or previously treated multiple myeloma that has progressed after prior therapy and requires new therapy. Outcomes for patients with disease progression is poor, therefore there is a need to develop new treatment options for RRMM.

Mezigdomide is an oral drug that targets a protein complex involved in breaking down other proteins. By changing the shape of this complex, mezigdomide helps it specifically target and destroy two important proteins that are crucial for the growth and function of blood cells and are involved in the development of multiple myeloma. Mezigdomide has a strong ability to bind to the protein complex, which helps in treating the cancer. If licensed, mezigdomide in combination with carfilzomib and dexamethasone, will provide an additional treatment option for RRMM patients.

Proposed Indication

Treatment of relapsed or refractory multiple myeloma (RRMM) after 1 or more prior treatments.[1]

Technology

Description

Mezigdomide (CC-92480/BMS-986348) is a novel oral cereblon E3 ligase modulator (CELMoD).[1,2] Like other CELMoD compounds, mezigdomide acts by altering the conformation of cereblon within the cullin 4A ring ligase–cereblon E3 ubiquitin ligase complex, thereby recruiting novel protein substrates for selective proteasomal degradation. These include two critical lymphoid transcription factors, Ikaros family zinc finger proteins 1 and 3, also known as Ikaros and Aiolos, which have important roles in the development and differentiation of haematopoietic cells, in multiple myeloma (MM) pathobiology, and in suppressing the expression of interferon-stimulating genes and T-cell stimulation. Among the CELMoD compounds, mezigdomide has the greatest cereblon-binding potency, as well as the greatest potency for the degradation of Ikaros and Aiolos and subsequent downstream antimyeloma effects.[3,4]

Oral mezigdomide in combination with intravenous (IV) carfilzomib and oral/IV dexamethasone is proposed for the treatment of RRMM. In the phase III trial (NCT05552976, SUCCESSOR-2) there are two stages. In Stage 1 ≥ 128 patients will be randomised 3:3:3:2 to one of three mezigdomide doses (1.0, 0.6, or 0.3mg) with carfilzomib and dexamethasone (MeziKd), or carfilzomib with dexamethasone (Kd). In Stage 2 ≈ 397 additional patients will be randomised 3:2 to MeziKd at the selected mezigdomide dose or to Kd for efficacy and safety analyses. (Stage 1 patients in the selected MeziKd dose cohort and Kd arm will also be included in these analyses).[1,3]

Key Innovation

Despite significant advances and improvements in overall survival, MM remains incurable, and additional treatments are needed.[5] Among today's standards of care, immunomodulatory drugs are commonly used in quadruplet and triplet regimens in newly diagnosed patients with MM and those with relapsed disease. However, resistance to these drugs can arise over the course of treatment; therefore, novel, more potent agents are being developed to restore and increase activity against relapsed MM, one of which is the investigational agent mezigdomide.[4]

This technology has demonstrated greater cereblon-binding affinity than the immunomodulatory drugs as well as being the most potent of the cereblon E3 ligase modulators. It has also recently demonstrated notable clinical activity in combination with dexamethasone in triple-class-refractory RRMM.[4,6] If licensed MeziKd will provide an additional treatment option for patients with RRMM.

Regulatory & Development Status

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

Dexamethasone currently has Marketing Authorisation in the EU/UK for a wide variety of disorders amenable to glucocorticoid therapy, as well as an adjunct in the control of cerebral oedema.[7]

Carfilzomib currently has Marketing Authorisation in the EU/UK in combination with daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone is indicated for the treatment of adult patients with MM who have received at least one prior therapy.[8]

Mezigdomide was awarded an orphan drug designation in the USA in 2019 for the treatment of MM.[9]

Mezigdomide is also in phase III/II clinical development for hepatic impairment and renal impairment.[10]

Patient Group

Disease Area and Clinical Need

MM, also known as myeloma, is a type of blood cancer that develops when there is a change in the DNA of plasma cells.[11,12] It's not known exactly what causes MM. However, there is a close link between MM and a condition called monoclonal gammopathy of unknown significance (MGUS). MGUS is where there is an excess of protein molecules, called immunoglobulins, in your blood; this does not cause any symptoms and does not need treatment. Every year, around 1 in every 100 people with MGUS go on to develop MM. MM is also more common in men and adults over 60 years old.[11] 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.[11] 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 multiple myeloma that has progressed after prior therapy and requires new therapy.[13] 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.[13] Treatment can often help to control the condition for several years but most cases of MM cannot be cured.[11]

MM is the 19th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-2018).[14] The age standardised incidence rate of MM in England is 12.3-12.8 and 7.6-7.9 per 100,000 amongst males and females respectively.[15] In England (2022-23) there were 155,822 finished consultant episodes (FCEs) and 150,740 admissions for MM (ICD-10 code C90.0), which resulted in 142,557 bed days and 99,552 FCE bed days.[16] In England (2017), there were 4,799 patients diagnosed with MM.[16] 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.[16]

Recommended Treatment Options

- National Institute for Health and Care Excellence (NICE) guidelines recommend the following treatment options for RRMM after at least one line of prior therapy:Selinexor with bortezomib and dexamethasone for previously treated MM[17]
- Lenalidomide with dexamethasone for people who have received two or more prior therapies.[18]
- Carfilzomib for previously treated MM[19]
- Carfilzomib with dexamethasone and lenalidomide for previously treated MM[20]
- Selinexor with dexamethasone after four or more treatments[21]
- 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[22]
- Ixazomib with lenalidomide and dexamethasone for adults who have had two or three lines of therapy[23]
- Isatuximab with 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[24]

- Panobinostat with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent[25]
- Pomalidomide with low-dose dexamethasone for adults who have received at least three treatments including both lenalidomide and bortezomib[26]

Clinical Trial Information

Trial	**SUCCESSOR-2;** NCT05552976; A Phase 3, Two-stage, Randomized, Multicentre, Open-label Study Comparing Mezigdomide (CC-92480/BMS-986348), Carfilzomib, and Dexamethasone (MeziKD) Versus Carfilzomib and Dexamethasone (Kd) in Participants With Relapsed or Refractory Multiple Myeloma (RRMM) **Phase III** - Recruiting **Locations:** Seven EU countries, UK, USA, Canada and other countries. **Primary completion date:** February 2026
Trial Design	Randomised, parallel assignment, open label.
Population	N=525 (estimated); participants with RRMM; adults aged 18 years and older who have received at least 1 prior line of therapy and have had prior exposure to lenalidomide and an anti-CD38 monoclonal antibody
Intervention(s)	**Stage 1:** One of three oral mezigdomide doses (1.0, 0.6, or 0.3mg) on 28-day (D) cycles (C) with mezigdomide on D1-21; 20 mg/m^2 IV carfilzomib (CFZ) on D1 of C1, then 56 mg/m^2 on D8 and 15 of C1, on D1, 8, and 15 of C2–12, and on D1 and 15 of ≥ C13; and 40 mg oral/IV dexamethasone (DEX) (20 mg optional in certain patient groups) on D1, 8, 15, and 22.[3] **Stage 2:** Mezigdomide with CFZ and DEX (MeziKd) at the selected mezigdomide dose or Kd for efficacy and safety analyses (Stage 1 patients in the selected MeziKd dose cohort and Kd arm will also be included in these analyses).[3]
Comparator(s)	**Active comparator for Stage 1 (CFZ with DEX Kd arm):** 28-D cycles with 20 mg/m^2 IV CFZ on D1 and 2 of C1, then 56 mg/m^2 on D8, 9, 15, and 16 of C1, and on D1, 2, 8, 9, 15, and 16 of ≥ C2; and 20 mg oral/IV DEX (10 mg optional in certain patient groups) on D1, 2, 8, 9, 15, 16, 22, and 23.[3]
Outcome(s)	**Primary outcome measure:** Progression-free Survival (PFS) up to approximately 5 years. See trial record for a list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03989414, EudraCT 2018-004767; A Phase 1/2, Multicenter, Open-label, Study to Determine the Recommended Dose and Regimen, and Evaluate the

	Safety and Preliminary Efficacy of CC-92480 in Combination With Standard Treatments in Subjects With Relapsed or Refractory Multiple Myeloma (RRMM) **Phase I/II** – Active, Not recruiting **Locations**: Seven EU countries, USA and Canada **Primary completion date**: November 2026
Trial Design	Non-randomised, parallel assignment, open label.
Population	N=424 (estimated); subjects with RRMM and newly diagnosed multiple myeloma (NDMM); adults aged 18 years and older
Intervention(s)	Mezigdomide along with specified doses of dexamethasone and various other drugs (bortezomib, carfilzomib, elotuzumab, isatuximab, or daratumumab) to multiple cohorts.
Comparator(s)	N/A
Outcome(s)	**Primary outcome measures:** • Establish the recommended dose and regimen by assessing dose-limiting toxicities over approximately 3 years. • Monitor the number of participants experiencing adverse events from the first visit until 28 days after the last subject discontinues treatment (up to 5 years). • Evaluate the overall response rate within the same 5-year period. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of mezigdomide is currently unknown.

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 in development. Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (GID-TA10918). Expected date of issue to be confirmed.
- NICE technology appraisal. Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after 4 or more treatments (TA970). May 2024.
- 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. Carfilzomib for previously treated multiple myeloma (TA657). November 2020.
- 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.
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Other Guidance

- European Society for Medical Oncology (ESMO). Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2021.[27]
- International Myeloma Working Group (IMWG). Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. 2021.[28]
- British Society of Haematology (BSH). Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. 2017.[29]

Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.