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Newcastle University

Health Technology Briefing
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Talquetamab for previously treated relapsed or refractory multiple myeloma

Company/Developer	Janssen-Cilag Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30897	NICE ID: 10733	UKPS ID: 662562

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Talquetmab is in clinical development for the treatment of relapsed or refractory multiple myeloma (MM), in patients who have received at least three prior lines of therapy. MM is a rare type of blood cancer that affects multiple areas of the body and is currently incurable. MM develops in the plasma cells of the bone marrow, which is found inside some of the larger bones, and affects the production of white and red blood cells as well as platelets. MM is a relapsing and remitting cancer and can be treated to give the patient periods that are symptom-free, but it eventually returns and develops resistance to previous treatments (refractory MM). The symptom free periods between relapses eventually become shorter each time until the disease becomes fatal. New treatment options can increase overall survival lengths of patients, giving more options to those who have become refractory to several treatments.

Talquetamab is a novel type of cancer medicine that binds the patient's immune cells to the abnormal MM cells to facilitate the killing of the cancer through an immune response. Talquetamab is administered via subcutaneous injection, allowing higher doses to be delivered to the patient while limiting adverse events. If licensed, talquetamab will offer a new treatment option for patients with relapsed or refractory MM who have already received at least three previous treatments.

Proposed Indication

Treatment of patients with relapsed or refractory multiple myeloma (MM).[1]

Technology

Description

Talquetamab (JNJ-64407564) is bispecific humanised monoclonal antibody against human CD3, a T-cell surface antigen, and human G-protein coupled receptor family C group 5 member D (GPRC5D), a tumour-associated antigen (TAA), with potential antineoplastic activity. Upon administration, talquetamab binds to both CD3 on T cells and GPRC5D expressed on certain tumour cells. This results in the cross-linking of T cells and tumour cells and induces a potent cytotoxic T-lymphocyte (CTL) response against GPRC5D-expressing tumour cells. GPRC5D is overexpressed on certain tumours, such as multiple myeloma, while minimally expressed on normal, healthy cells, and plays a key role in tumour cell proliferation.[2]

Talquetamab is in clinical development for patients with relapsed/ refractory MM who have previously received greater than or equal to 3 prior lines of therapy. In the phase II clinical trial (NCT04634552), talquetamab will be administered subcutaneously (SC) at a recommended Phase 2 dose (RP2D).[1]

Key Innovation

Talquetamab is the only bispecific antibody targeting both GPRC5D and CD3 on T cells. Results from preclinical studies demonstrate that talquetamab induces T-cell-mediated killing of GPRC5D-expressing multiple myeloma cells through the recruitment and activation of CD3-positive T-cells and inhibits tumour formation and growth.[3]

Subcutaneous delivery of talquetamab allows larger doses to be administered to patients than intravenous delivery, giving a favourable efficacy and safety profile and less of a treatment burden for the patient.[4] If licensed, talquetamab will offer a new treatment option for patients with relapsed/ refractory MM who have received at least three prior treatment lines.

Regulatory & Development Status

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

Talquetamab was granted PRIME designation for the treatment of adult patients with relapsed or refractory multiple myeloma, who previously received ≥3 prior lines of therapy, by the EMA in January 2021.[5]

Patient Group

Disease Area and Clinical Need

Multiple myeloma (MM) is a type of cancer that develops in the plasma cells of the bone marrow, causing an abnormal build-up of cells and paraprotein, damaging the bones and affecting the production of healthy blood cells.[6,7] MM is an incurable relapsing-remitting cancer, meaning there are periods of symptoms and/or complications which require treatment, followed by periods of remission or plateau

where there are no symptoms and does not require treatment. Most patients develop multiple drug resistance, often through mutation or alteration in the expression of the drug target, resulting in the need to discover and target novel pathways.[8] Triple-class refractory MM is one in which the MM is resistant to all three classes of standard myeloma therapies.[9]There is often no known cause of MM, but there are several known risk factors. Prevalence is highest in men and is most often diagnosed in adults around the age of 70.[6] Race and weight can also be risk factors, as well as immune conditions such as HIV and monoclonal gammopathy of undetermined significance (MGUS).[10] Every year 1 in 100 people with MGUS develop MM, and people with a family history of MGUS or MM are more likely to develop MM, showing a genetic influence.[6] MM is often asymptomatic in the early stages and is often found when patients are undergoing routine tests, but it progresses to affect multiple organ systems.[6,10] In later stages, symptoms include persistent bone pain, fatigue and weakness, shortness of breath, unexplained bruising, recurrent infections and kidney damage.[6,11]

MM is the 19th most common cancer in the UK and accounts for 15% of new blood cancer diagnosis and 2% of all cancer cases.[7,12] Each year in the UK there are approximately 6,000 new MM cases, with around 3,100 deaths (2016-18). The five-year survival rate in England is 52.3%, dropping to 29% survival over 10 years (2013-17).[12] In England (2020-21), there were 107,457 finished consultant episodes (FCE) for MM (ICD-10 code: C90.0), with 103,209 hospital admissions that resulted in 92,913 day cases and 66,906 FCE bed days.[13]

Recommended Treatment Options

Treatment for relapsed MM depends on how long the patient was in remission for; the previous treatment received and the general health of the patient. Treatment options usually involve the use of targeted cancer drugs; a combination of chemotherapy drugs, with or without targeted cancer drugs; and a steroid.[14]

NICE guidelines recommend the following treatment options for relapsed or refractory MM:[15]

- Ixazomib, with lenalidomide and dexamethasone is recommended for patients who have already received 2 or 3 lines of therapy.
- Panobinostat in combination with bortezomib and dexamethasone is recommended for adult patients with relapsed and/or refractory MM who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent.
- Lenalidomide in combination with dexamethasone is recommended in people who have received 2 or more prior therapies.
- Isatuximab, plus pomalidomide and dexamethasone, is recommended for relapsed and refractory MM in adults who have had lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last treatment, only if they have had 3 previous lines of treatment.
- Daratumumab monotherapy is recommended for treating relapsed and refractory MM in adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies.
- Pomalidomide, in combination with low-dose dexamethasone, is recommended for treating MM in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib.

Clinical Trial Information

Trial	**TALMMY1001-PT3;** NCT04634552, 2017-002400-26; A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects With Relapsed or Refractory Multiple Myeloma **Phase II** - ongoing **Location(s):** 6 EU countries, USA, China and other countries **Primary completion date:** August 2023
Trial Design	Non-randomized, parallel assignment, open label
Population	N= 293(estimated); Subjects with multiple myeloma who have previously received greater than or equal to (>=) 3 prior lines of therapy; aged 18 years and over
Intervention(s)	Participants will receive talquetamab (SC) at a recommended Phase 2 dose selected after review of safety, efficacy, PK, and pharmacodynamic data from Part 1 and Part 2 of this study
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: Overall Response Rate (ORR) [Time Frame: Up to 2 years and 10 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of talquetamab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 3 therapies (ID2701). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Elotuzumab for multiple myeloma (ID966). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Idecabtagene vicleucel for treating relapsed and refractory multiple myeloma in people who have received at least 3 prior therapies (ID1442). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Pelareorep for treating relapsed or refractory multiple myeloma (ID1028). Expected publication date to be confirmed
- NICE technology appraisal guidance in development. Pembrolizumab for previously treated multiple myeloma (ID1139). Expected publication date to be confirmed.

- NICE technology appraisal guidance in development. Plitidepsin in combination with dexamethasone for treating relapsed or refractory multiple myeloma (ID1081). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Selinexor with bortezomib and low dose dexamethasone for treating relapsed or refractory multiple myeloma (ID3797). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Melphalan flufenamide with dexamethasone for treating relapsed or refractory multiple myeloma (ID3862). Expected publication date January 2023.
- NICE technology appraisal guidance in development. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma (ID2709). Expected publication date October 2022.
- NICE technology appraisal guidance in development. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) (ID1635). Expected publication date March 2022.
- NICE technology appraisal guidance in development. Ciltacabtagene autoleucel for treating relapsed or refractory multiple myeloma (ID3816). Expected publication date February 2022.
- NICE technology appraisal. Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma (TA695). April 2021.
- NICE technology appraisal. Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (TA658). November 2020.
- NICE technology appraisal. Carfilzomib for previously treated multiple myeloma (TA657). November 2020.
- NICE technology appraisal. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). March 2018.
- NICE technology appraisal. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE guideline. Myeloma: diagnosis and management (NG35). October 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Bendamustine for relapsed multiple myeloma (all ages). 2020. 200604/P
- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 2017. 16068/P
- NHS England. Clinical Commissioning Policy: Intrathecal Drug Delivery for Cancer Pain. 2015. D08/P/b
- NHS England. Clinical Commissioning Policy: Haematopoietic stem Cell Transplantation (HSCT) (All ages): Revised. 2015. B04/P/a
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B/15/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

- British Society for Haematology (BSH) and the UK Myeloma Forum (UKMF). Guidelines on the diagnosis, investigation and initial treatment of myeloma. 2021.[16]
- European Society of Medical Oncology (ESMO). Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[17]
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: multiple myeloma, version 3. 2020.[18]
- American Society of Clinical Oncology. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. 2019.[19]
- NHS England. Manual for prescribed specialist services. Chapter 29: blood and marrow transplantation services (adults and children); Chapter 105: specialist cancer services (adults). 2018/19.[20]
- NHS England. National chemotherapy algorithms – multiple myeloma. 2015.[21]
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A report from IMWG. 2015.[22]

Additional Information

References

- 1 ClinicalTrials.gov. *A Study of Talquetamab in Participants With Relapsed or Refractory Multiple Myeloma*. *Trial ID: NCT04634552*. 2020. Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/NCT04634552 [Accessed December 1st, 2021].
- 2 National Cancer Institute. *Talquetamab.* 2021. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/talquetamab?redirect=true [Accessed December 20th, 2021].
- 3 Johnson & Johnson. *Janssen Presents Updated Results Evaluating First-in-Class Talquetamab (GPRC5DxCD3 Bispecific Antibody) in Heavily Pretreated Patients with Multiple Myeloma.* 2021. Available from: https://www.jnj.com/janssen-presents-updated-results-evaluating-first-in-class-talquetamab-gprc5dxcd3-bispecific-antibody-in-heavily-pretreated-patients-with-multiple-myeloma [Accessed December 12th, 2021].
- 4 Berdeja JG, Krishnan AY, Oriol A, van de Donk NWCJ, Rodríguez-Otero P, Askari E, et al. Updated results of a phase 1, first-in-human study of talquetamab, a G protein-coupled receptor family C group 5 member D (GPRC5D) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM). *Journal of Clinical Oncology*. 2021 2021/05/20;39(15_suppl):8008-. Available from: https://doi.org/10.1200/JCO.2021.39.15_suppl.8008.
- 5 EMA. *Recommendations on eligibility to PRIME scheme.* 2021. Available from: https://www.ema.europa.eu/en/documents/chmp-annex/recommendations-eligibility-prime-scheme-adopted-chmp-meeting-25-29-january-2021_en-0.pdf [Accessed December 1st, 2021].

- 6 NHS. *Overview: Multiple myeloma.* 2021. Available from: https://www.nhs.uk/conditions/multiple-myeloma/ [Accessed December 1st, 2021].
- 7 Myeloma UK. *What is myeloma?* 2021. Available from: https://www.myeloma.org.uk/understanding-myeloma/what-is-myeloma/ [Accessed December 6th, 2021].
- 8 Robak P, Drozdz I, Szemraj J, Robak T. Drug resistance in multiple myeloma. *Cancer treatment reviews*. 2018;70 119-208. Available from: https://doi.org/10.1016/j.ctrv.2018.09.001.
- 9 Renton C. *What Is Triple-Refractory Multiple Myeloma?* 2021. Available from: https://www.verywellhealth.com/triple-refractory-multiple-myeloma-5113498 [Accessed December 17th, 2021].
- 10 Cancer Research UK. *Myeloma.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/myeloma [Accessed December 1st, 2021].
- 11 Myeloma UK. *Symptoms & complications.* 2021. Available from: https://www.myeloma.org.uk/understanding-myeloma/symptoms-and-complications/ [Accessed December 1st, 2021].
- 12 Cancer Research UK. *Myeloma statistics.* 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Zero [Accessed December 6th, 2021].
- 13 NHS Digital Office for National Statistics. *Hospital Admitted Patient Care Activity, 2020-21: Diagnosis.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21#chapter-index [Accessed 18/11/21].
- 14 Cancer Research UK. *Treatment options.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/myeloma/treatment/treatment-decisions [Accessed December 17th, 2021].
- 15 NICE. *Myeloma overview.* 2021. Available from: https://pathways.nice.org.uk/pathways/myeloma [Accessed December 6th, 2021].
- 16 Sive J, Cuthill K, Hunter H, Kazmi M, Pratt G, Smith D, et al. Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. *British Journal of Haematology*. 2021;193(2):245-68. Available from: https://doi.org/10.1111/bjh.17410.
- 17 Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2021;32(3):309-22. Available from: https://doi.org/10.1016/j.annonc.2020.11.014.
- 18 Kumar SK, Callander NS, Adekola K, Anderson L, Baljevic M, Campagnaro E, et al. Multiple Myeloma, Version 3.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*. 2020 01 Dec. 2020;18(12):1685-717. Available from: https://doi.org/10.6004/jnccn.2020.0057.
- 19 Mikhael J, Ismaila N, Cheung MC, Costello C, Dhodapkar MV, Kumar S, et al. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. *Journal of Clinical Oncology*. 2019;37(14):1228-63. Available from: https://doi.org/10.1200/jco.18.02096.
- 20 NHS England. *Manual for Prescribed Specialised Services 2018/19.* 2018/19. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual.pdf [Accessed December 6th, 2021].
- 21 Thomson D. *National chemotherapy algorithms- multiple myeloma.* 2015. Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-

consultation/user_uploads/chemothrpy-algrthms-mltpl-myeloma.pdf [Accessed December 6th, 2021].

- 22 Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *Journal of Clinical Oncology*. 2015;33(26):2863-9. Available from: https://doi.org/10.1200/jco.2015.61.2267.

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