Health Technology Briefing
February 2026

Nemtabrutinib for previously untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma

Company/Developer	Merck Sharp & Dohme Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 36269	NICE ID: Not available	UKPS ID: 674896

Licensing and Market Availability Plans

Currently in phase III clinical trial

Summary

Nemtabrutinib is currently being developed for previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) without TP53 (a type of protein seen in cancer cells) aberrations. CLL is a rare type of cancer that affects the blood and the spongy inner part of the bone that produces red and white blood cells, also known as bone marrow. CLL and SLL are the same disease, but whereas in CLL the cancer cells are mostly found in the blood or bone marrow, in SLL they most commonly appear in the lymph nodes, which are small lumps of tissue that contain white blood cells. In both CLL and SLL, too many white blood cells are produced that are developing abnormally. The cause of CLL or SLL is unclear. Currently available treatments have been associated with resistance and toxicity, therefore an unmet need exists for novel therapies with manageable safety profiles and better efficacy outcomes.

Nemtabrutinib works by blocking the action of an enzyme called Bruton's tyrosine kinase (BTK) in cancer cells and is administered orally (by mouth). By inhibiting BTK, nemtabrutinib helps to stop or slow down the growth and spread of cancer cells in the body. Nemtabrutinib is designed to block the action of BTK in a different way from other BTK inhibitors, thereby overcoming problems with known resistance in this class of medicines. If licensed (approved), nemtabrutinib could offer an additional treatment option for adult patients with CLL or SLL without TP53 aberrations, who have not previously been treated.

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

Previously untreated chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) without tumour protein (TP)53 aberrations.[1]

Technology

Description

Nemtabrutinib (MK-1026, ARQ 531) is an investigational oral, reversible, non-covalent Bruton's tyrosine kinase (BTK) inhibitor that suppresses oncogenic B-cell receptor signalling with activity against wild-type BTK and BTK pathway mutants.[2,3] BTK is a key signalling molecule in the B-cell receptor pathway which is important for B-cell proliferation and survival.[4] Nemtabrutinib has additional activity against Src family kinases and kinases related to extracellular signal-regulated kinases (ERK) signalling. It is hypothesised that targeting additional kinases would improve global inhibition of signalling pathways, thereby producing more robust responses including effectiveness in BTK inhibitor naïve CLL.[5]

Nemtabrutinib is currently in clinical development for previously untreated CLL and SLL without TP53 aberrations in adult patients. In the phase III clinical trial (NCT05624554), participants will receive oral nemtabrutinib 65mg daily until disease progression, unacceptable toxicity, or the discontinuation criteria are met.[1]

Key Innovation

Relapse or disease progression during treatment with BTK inhibitors in patients with B-cell malignancies is commonly associated with acquired resistance.[4] BTK mutations associated with ibrutinib resistance occur at the C481 amino acid to which ibrutinib irreversibly binds, whereas phospholipase C gamma 2 (*PLCγ2)* mutations occur preferentially in the autoinhibitory domain of PLCγ2.[5] Nemtabrutinib is a non-covalent, potent inhibitor of both wild type and C481-mutated BTK.[6] It aims to address a common mechanism of resistance with currently available irreversible, covalent BTK inhibitors by binding in an alternative way to the BTK protein.[7] Additionally, treatment with some currently available BTK inhibitors have been associated with uncommon substantial toxicities, drug resistance, and low complete remission rates. Therefore, an unmet need exists for treatment options with manageable safety profiles and better efficacy outcomes.[8]

If licensed, nemtabrutinib could offer an additional treatment option for adults with previously untreated CLL and SLL without TP53 aberrations.

Regulatory & Development Status

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

Nemtabrutinib as a monotherapy is in phase II clinical development for the treatment of other haematologic malignancies:[9,10]

- CLL or SLL with or without TP53 mutations
- Non-Hodgkin's lymphoma
- Waldenström's macroglobulinaemia
- Diffuse large B cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Richter transformation lymphoma

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Nemtabrutinib has an orphan drug designation in the USA granted in 2020 for the treatment of CLL or SLL.[11]

Patient Group

Disease Area and Clinical Need

CLL is a rare type of cancer that affects the blood and bone marrow, and it usually progresses slowly.[12] In CLL, the bone marrow produces too many lymphocytes that are not fully developed and do not work properly. CLL and SLL are the same disease, but whereas in CLL the cancer cells are mostly found in the blood or bone marrow, in SLL they most commonly appear in the lymph nodes. Most people have abnormal cells in the lymph nodes, spleen, blood and bone marrow therefore SLL and CLL are now considered to be the same condition. [13] Over time this can cause a range of problems, such as an increased risk of picking up infections, persistent tiredness, swollen glands in the neck, armpits or groin, unusual bleeding or bruising, night sweats and unintentional weight loss.[14] The risk increases with age, and it is very rare in people under 40. Although the cause is unclear, the risk increases with a family history of CLL.[12]

Around 4,500 people are diagnosed with CLL/SLL every year in the UK.[15] CLL accounted for 1% of all new cancer cases in the UK (2017-2019). The incidence rates for CLL are highest in people aged 85 to 89, and around 41% of all new CLL cases in the UK are diagnosed in people aged 75 and over.[16] CLL/SLL is rare in young people.[15] In England (2017), there were 4,226 patients diagnosed with lymphoid leukaemia and 1,085 deaths registered where lymphoid leukaemia was the underlying cause.[17] There are around 980 CLL deaths in the UK every year (2017-2019).[18] The age standardised incidence rate of lymphoid leukaemia in England is 10.7 and 5.6 per 100,000 amongst males and females respectively.[17] In England (2024-2025), there were 21,984 finished consultant episodes (FCE) and 20,894 admissions for CLL (ICD-10 code C91.1) which resulted in 13,450 FCE bed days and 18,789 day cases.[19]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following for untreated CLL:[20-26]

- obinutuzumab with chlorambucil
- rituximab
- bendamustine
- fludarabine
- ibrutinib with venetoclax
- venetoclax with obinutuzumab
- idelalisib

There are currently no NICE recommended treatment options for untreated SLL.

Clinical Trial Information

Trial	**BELLWAVE-008 (MK-1026-008),** NCT05624554, EudraCT 2021-004453-23; A phase 3, randomized study to compare the efficacy and safety of nemtabrutinib versus chemoimmunotherapy for previously untreated chronic lymphocytic leukemia/small lymphocytic lymphoma without TP53 aberrations **Phase III:** Active, not recruiting

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	Locations: Six EU countries, USA and other countries **Primary completion date:** May 2027
Trial Design	Randomised, parallel assignment, single masking
Population	N = 300 (estimated); adults aged 18 years and older with confirmed diagnosis of CLL or SLL without TP53 aberrations; who have been previously untreated
Intervention(s)	Oral nemtabrutinib (65mg)
Comparator(s)	• Intravenous (IV) fludarabine + IV cyclophosphamide + IV rituximab • IV bendamustine + IV rituximab or IV rituximab biosimilars
Outcome(s)	Primary outcome: Progression-free survival (PFS) per international workshop on chronic lymphocytic leukaemia (iwCLL) criteria 2018 as assessed by blinded independent central review (BICR) [time frame: up to approximately 49 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of nemtabrutinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (GID-TA11495). Expected publication date: March 2026
- NICE technology appraisal. Acalabrutinib with venetoclax and obinutuzumab for untreated chronic lymphocytic leukaemia (GID-TA11087). Expected date of issue to be confirmed.
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- NICE technology appraisal. Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia (GID-TA11230). Expected date of issue to be confirmed.
- NICE technology appraisal. Pirtobrutinib for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma (GID-TA11501). Expected date of issue to be confirmed.
- NICE technology appraisal. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (TA1119). January 2026.
- NICE technology appraisal. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia (TA891). May 2023.
- NICE technology appraisal. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015.

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- NICE technology appraisal. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. (TA216). February 2011.
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NHS England (Policy/Commissioning) Guidance

- 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.

Other Guidance

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