# Health Technology Briefing
# May 2026

# Nemtabrutinib for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma

| Company/Developer | Merck Sharp & Dohme Ltd |
|---|---|

☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 38261 | NICE ID: Not available | UKPS ID: 675054 |
|---|---|---|

## Licensing and Market Availability Plans

Currently in phase III clinical trial

## Summary

Nemtabrutinib is being developed for previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). 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. Current treatments often stop working or cause bad side effects, so there is a need for new, safer and more effective medicines.

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, 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.

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

## Proposed Indication

Untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (CLL/SLL).[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 untreated CLL and SLL in adult patients. In the phase III clinical trial (BELLWAVE-011, NCT06136559), participants will receive oral nemtabrutinib 65mg once daily until disease progression, unacceptable toxicity, or other discontinuation criteria are met.[1,6]

### Key Innovation

Relapse or disease progression during treatment with BTK inhibitors in patients with B-cell malignancies is commonly associated with acquired resistance.[4] Most patients eventually relapse when treated with the currently approved covalent BTK inhibitors (cBTKi), commonly through acquisition of the C481S BTK mutation. Nemtabrutinib is a non-covalent BTK inhibitor developed to target and inhibit C481S mutant BTK, and is a potent inhibitor of both wild type and C481-mutated BTK.[7,8] Nemtabrutinib 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.[9] This mechanism does not require C481, while allowing non-covalent BTKi to overcome the resistance that occurs from the BTK C481 point mutations that emerge in patients as a mechanism of resistance to cBTKi.[10] Additionally, treatment with some currently available BTK inhibitors has 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.[11]

If licensed, nemtabrutinib could offer an additional treatment option for adults with previously untreated CLL and SLL.

### 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 such as:[12]

- CLL or SLL without TP53 mutations
- non-Hodgkin's lymphoma
- Waldenström's macroglobulinaemia
- diffuse large B cell lymphoma
- follicular lymphoma
- mantle cell lymphoma
- Richter transformation lymphoma

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

Nemtabrutinib has an orphan drug designation from the US Food and Drug Administration which was granted in 2020 for the treatment of CLL or SLL.[13]

## 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.[14] 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.[15] 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.[16] The risk of developing CLL 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.[14]

Around 4,500 people are diagnosed with CLL/SLL every year in the UK.[17] 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.[18] CLL/SLL is rare in young people.[17] In England (2017), there were 4,226 patients diagnosed with lymphoid leukaemia and 1,085 deaths registered where lymphoid leukaemia was the underlying cause.[19] There are around 980 CLL deaths in the UK every year (2017-2019).[20] The age standardised incidence rate of lymphoid leukaemia in England is 10.7 and 5.6 per 100,000 amongst males and females respectively.[19] 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.[21]

### Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following for untreated CLL:[22-28]

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

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

## Clinical Trial Information

| | |
|---|---|
| Trial | **BELLWAVE-011 (MK-1026-011),** NCT06136559; A phase 3, randomised study to compare nemtabrutinib versus comparator (investigator's choice of ibrutinib or acalabrutinib) in participants with untreated CLL/SLL<br>**Phase III:** Recruiting<br>**Locations:** Nine EU countries, UK, USA, Canada and other countries<br>**Primary completion date:** September 2032 |

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

| | |
|---|---|
| Trial Design | Randomised, parallel assignment, open label |
| Population | N = 1200 (estimated); adults aged 18 years and older with confirmed diagnosis of active CLL or SLL; who have been previously untreated |
| Intervention(s) | Oral nemtabrutinib 65mg, once daily.[6] |
| Comparator(s) | • Oral ibrutinib 420mg, once daily OR<br>• Oral acalabrutinib, 100mg twice daily.[6] |
| Outcome(s) | Primary outcomes:<br>• Objective response rate per chronic lymphocytic leukemia (iwCLL) criteria 2018 as assessed by blinded independent central review (BICR) [time frame: up to approximately 33 months]<br>• Progression-free survival (PFS) per iwCLL criteria 2018 as assessed by BICR [time frame: up to approximately 104 months]<br>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. Acalabrutinib with venetoclax and obinutuzumab for untreated chronic lymphocytic leukaemia (GID-TA11087). 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. Zanubrutinib for untreated chronic lymphocytic leukaemia (GID-TA10966). Expected date of issue to be confirmed.
- NICE technology appraisal. Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia (GID-TA11230). Expected date of issue April 2026.
- 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. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia (TA891). May 2023.
- NICE technology appraisal. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (TA663). December 2020.
- NICE technology appraisal. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343). June 2015

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

- NICE technology appraisal. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. (TA216). February 2011.
- NICE technology appraisal. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (TA174). July 2009.
- NICE technology appraisal. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (TA119). February 2007.

### 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

- Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H et al. (British Society of Haematology) Guideline for the treatment of chronic lymphocytic leukaemia. 2022.[29]
- Wierda WG, Brown J, Abramson JS, Awan F, Bilgrami SF, Bociek G et al. NCCN Guidelines Insights: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 3.2022. 2022.[30]
- Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP et al. Chronic lymphocytic leukaemia: European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[31]
- Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner et al. H. International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. 2018.[32]

## References

1 ClinicalTrials.gov. *A Study of Nemtabrutinib (MK-1026) Versus Comparator (Investigator's Choice of Ibrutinib or Acalabrutinib) in First Line (1L) Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL) (MK-1026-011/BELLWAVE-011)*. 2023. Available from: https://clinicaltrials.gov/study/NCT06136559 [Accessed 29 September 2025].

2 Clival Database. *Merck announces phase 3 trial initiations for four investigational candidates from its promising haematology and oncology pipeline*. 2024. Available from: https://clival.com/news/merck-announces-phase-3-trial-initiations-for-four-investigational-candidates-from-its-promising-haematology-and-oncology-pipeline [Accessed 29 September 2025].

3 Woyach J, Flinn IW, Awan FT, Eradat H, Brander D, Tees M, et al. P682: NEMTABRUTINIB (MK-1026), A NON-COVALENT INHIBITOR OF WILD-TYPE AND C481S MUTATED BRUTON TYROSINE KINASE FOR B-CELL MALIGNANCIES: EFFICACY AND SAFETY OF THE PHASE 2 DOSE-EXPANSION BELLWAVE-001 STUDY. *Hemasphere*. 2022;6:578-9. Available from: https://doi.org/10.1097/01.HS9.0000845612.25766.0c.

4 Shirley M. Bruton Tyrosine Kinase Inhibitors in B-Cell Malignancies: Their Use and Differential Features. *Targeted Oncology*. 2022;17(1):69-84. Available from: https://doi.org/10.1007/s11523-021-00857-8.

5 Reiff SD, Mantel R, Smith LL, Greene JT, Muhowski EM, Fabian CA, et al. The BTK Inhibitor ARQ 531 Targets Ibrutinib-Resistant CLL and Richter Transformation. *Cancer Discovery*. 2018;8(10):1300-15. Available from: https://doi.org/10.1158/2159-8290.Cd-17-1409.

6 Tadmor T, Eyre TA, Benjamini O, Chaudhry A, Shen J, Leng S, et al. CLL-414 Phase 3 BELLWAVE-011 Study: Nemtabrutinib Versus Ibrutinib or Acalabrutinib in Previously

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

Untreated Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL). *Clinical Lymphoma Myeloma and Leukemia*. 2024;24:S352-S3. https://www.sciencedirect.com/science/article/pii/S2152265024012783.

7 Woyach JA, Flinn IW, Awan FT, Eradat H, Brander D, Tees M, et al. Efficacy and Safety of Nemtabrutinib, a Wild-Type and C481S-Mutated Bruton Tyrosine Kinase Inhibitor for B-Cell Malignancies: Updated Analysis of the Open-Label Phase 1/2 Dose-Expansion Bellwave-001 Study. *Blood*. 2022;140(Supplement 1):7004-6. Available from: https://doi.org/10.1182/blood-2022-163596.

8 Gordon B, Muhowski E, Ravikrishnan J, Benrashid S, Mitchell A, He A, et al. Targeting Covalent and Non-Covalent Btki-Resistant CLL Using the Dual Irreversible/Reversible 4 th Generation BTK Inhibitor LP-168. *Blood*. 2023;142(Supplement 1):416-. Available from: https://doi.org/10.1182/blood-2023-178259.

9 Neuro Central. *Merck Announces Phase 3 Trial Initiations for Four Investigational Candidates From its Promising Hematology and Oncology Pipeline*. 2024. Available from: https://www.neuro-central.com/merck-announces-phase-3-trial-initiations-for-four-investigational-candidates-from-its-promising-hematology-and-oncology-pipeline/ [Accessed 29 September 2025].

10 Montoya S, Thompson MC. Non-Covalent Bruton's Tyrosine Kinase Inhibitors in the Treatment of Chronic Lymphocytic Leukemia. *Cancers*. 2023;15(14). Available from: https://doi.org/10.3390/cancers15143648.

11 Tadmor T, Eyre TA, Benjamini O, Chaudhry A, Shen J, Leng S, et al. Nemtabrutinib Versus Ibrutinib or Acalabrutinib for Untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The Phase 3, Open-Label, Randomized Bellwave-011 Study. *Blood*. 2024;144:1875.2. https://www.sciencedirect.com/science/article/pii/S0006497124110944.

12 ClinicalTrials.gov. *Nemtabrutinib | Phase: 2, 3 | Funded by Industry*. 2021. Available from: https://clinicaltrials.gov/search?intr=Nemtabrutinib&aggFilters=funderType:industry,phase:2%203 [Accessed 29 September 2025].

13 United States Food & Drug Administration. *Search Orphan Drug Designations and Approvals*. 2020. Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=787120 [Accessed 29 September 2025].

14 National Health Service (NHS). *What is chronic lymphocytic leukaemia?* 2023. Available from: https://www.nhs.uk/conditions/chronic-lymphocytic-leukaemia/ [Accessed 29 September 2025].

15 Macmillan Cancer Support. *Small lymphocytic lymphoma (SLL)*. 2021. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/non-hodgkin/types/small-lymphocytic [Accessed 29 September 2025].

16 National Health Service (NHS) inform. *Chronic lymphocytic leukaemia*. 2025. Available from: https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/chronic-lymphocytic-leukaemia/ [Accessed 29 September 2025].

17 Lymphoma Action. *Who gets CLL/SLL?* 2023. Available from: https://lymphoma-action.org.uk/sites/default/files/media/documents/2023-11/LYMweb0091CLL2023v7%20PDF.pdf#:~:text=Around%204%2C500%20people%20are%20diagnosed%20with%20CLL%2FSLL%20every,72%20years.%20CLL%2FSLL%20is%20rare%20in%20young%20people. [Accessed 29 September 2025].

18 Cancer Reasearch UK. *Chronic lymphocytic leukaemia (CLL) incidence*. 2025. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll [Accessed 29 September 2025].

19 Office for National Statistics. *Cancer registration statistics, England*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsa

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

nddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 29 September 2025].

20 Cancer Reasearch UK. *Chronic lymphocytic leukaemia (CLL) mortality*. 2025. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll#heading-One [Accessed 29 September 2025].

21 National Health Service (NHS) England. *Primary diagnosis: 4 character*. 2025. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2FCC%2FEA025D%2Fhosp-epis-stat-admi-diag-2024-25-tab.xlsx&wdOrigin=BROWSELINK [Accessed 5 November 2025].

22 National Institute for Health and Care Excellence (NICE). *Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia*. 2015. Available from: https://www.nice.org.uk/guidance/ta343 [Accessed 29 September 2025].

23 National Institute for Health and Care Excellence (NICE). *Rituximab for the first-line treatment of chronic lymphocytic leukaemia*. 2009. Available from: https://www.nice.org.uk/guidance/ta174 [Accessed 29 September 2025].

24 National Institute for Health and Care Excellence (NICE). *Bendamustine for the first-line treatment of chronic lymphocytic leukaemia*. 2011. Available from: https://www.nice.org.uk/guidance/ta216 [Accessed 29 September 2025].

25 National Institute for Health and Care Excellence (NICE). *Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia*. 2007. Available from: https://www.nice.org.uk/guidance/ta119 [Accessed 29 September 2025].

26 National Institute for Health and Care Excellence (NICE). *Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia*. 2023. Available from: https://www.nice.org.uk/guidance/ta891 [Accessed 29 September 2025].

27 National Institute for Health and Care Excellence (NICE). *Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia*. 2020. Available from: https://www.nice.org.uk/guidance/ta663 [Accessed 29 September 2025].

28 National Institute for Health and Care Excellence (NICE). *Idelalisib for treating chronic lymphocytic leukaemia*. 2015. Available from: https://www.nice.org.uk/guidance/ta359 [Accessed 29 September 2025].

29 Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H, et al. Guideline for the treatment of chronic lymphocytic leukaemia. *British Journal of Haematology*. 2022;197(5):544-57. https://onlinelibrary.wiley.com/doi/abs/10.1111/bjh.18075.

30 Wierda WG, Brown J, Abramson JS, Awan F, Bilgrami SF, Bociek G, et al. NCCN Guidelines® Insights: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 3.2022: Featured Updates to the NCCN Guidelines. *Journal of the National Comprehensive Cancer Network*. 2022;20(6):622-34. Available from: https://doi.org/10.6004/jnccn.2022.0031.

31 Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2021;32(1):23-33. https://www.sciencedirect.com/science/article/pii/S092375342042469X.

32 Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-60. Available from: https://doi.org/10.1182/blood-2017-09-806398.

***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.***

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.