NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
January 2022

Zanubrutinib for previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma

Company/Developer	BeiGene UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 20512	NICE ID: 10750	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) are types of cancer in which too many white blood cells (B-cells) are produced, these cells build up in the lymph nodes, blood, and bone marrow. As these cells develop abnormally, they are unable to function, fight infection and reduce the production of healthy blood cells. These diseases are chronic and develop slowly. Treatment is complex and depends on several factors, including the extent of disease, previous treatment, patient's age, symptoms, and general state of health. There is an unmet need to develop more effective, and better tolerated treatment options to improve long-term outcomes for patients.

Zanubrutinib is an oral medication taken once or twice a day and is being developed for the first line treatment of patients with CLL/SLL. Zanubrutinib works by blocking a protein called Bruton's tyrosine kinase in the abnormal B-cells which prevents the growth of these cells. Preliminary analysis of recent studies have demonstrated that Zanubrutinib improves treatment outcomes and is well tolerated by previously untreated patients with CLL/SLL when compared with some standard chemo-immunotherapies. If licenced, zanubrutinib would provide an additional first line treatment option for patients that is well tolerated.

Proposed Indication

First line treatment of adults with previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).[1]

Technology

Description

Zanubrutinib (Brukinsa, BGB-3111) is a potent and highly selective small molecule Bruton's tyrosine kinase (BTK) inhibitor.[2] Zanubrutinib works by binding to and inhibiting BTK which prevents the activation of the B-cell antigen receptor (BCR) signalling pathway. This inhibits B-cell activation and the growth of malignant B-cells which overexpress BTK (which plays an important role in the development, activation, signalling, proliferation, and survival of B-lymphocytes).[2,3]

Zanubrutinib is in phase III clinical development (NCT04170283; NCT03336333) for previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). It is given as 160mg twice daily.[1,4] The recommended total daily dose of zanubrutinib is 320 mg. The daily dose may be taken either once daily (four 80 mg capsules) or divided into two doses of 160 mg twice daily (two 80 mg capsules).[5]

Key Innovation

While several standard chemo-immunotherapies are available for CLL/SLL, some patients respond poorly to some of these therapies in addition to significant adverse effects, necessitating the need for more effective, and better tolerated treatment options.[6,7]

In an interim analysis of phase III study (SEQUOIA, NCT03336333) zanubrutinib demonstrated superiority in progression-free survival over chemoimmunotherapy as a first line treatment. It was active and well tolerated by previously untreated patients, with an 18-month estimated progression-free survival (PFS) rate of 88.6% and overall survival of 95.1%.[6,7]

Regulatory & Development Status

Zanubrutinib has received both EMA and MHRA Marketing Authorisation (MA) for the treatment of adults with Waldenström's macroglobulinaemia who have not been treated before and who cannot receive chemo-immunotherapy or in patients who have received at least one prior therapy.[8,9]

Zanubrutinib is in phase III/II clinical development for mantle cell lymphoma, marginal zone lymphoma, and lupus nephritis, amongst others.[10]

Patient Group

Disease Area and Clinical Need

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia, which affects blood cells in the bone marrow and progresses slowly over time. In CLL too many white blood cells (lymphocytes) are produced, however these are not fully developed and do not function properly. Symptoms include regular infections, anaemia, tiredness, bleeding and bruising easily, high temperature, night sweats, swollen glands and unintentional weight loss.[11,12] Small lymphocytic lymphoma (SLL) is considered the same condition as CLL, as most CLL/SLL patients have abnormal lymphocytes in locations that overlap with the two

conditions, including lymph nodes, spleen, blood and bone marrow.[13] Risk factors include increased age, being male, having a close relative with CLL, and European descent.[14]

In England, 2020-21, there were 17,230 finished consultant episodes (FCE) of CLL of B-cell type (ICD-10 code C91.1) resulting in 13,911 day cases and 10,364 FCE bed days.[15] In the UK, there were around 3,800 new cases of CLL every year (2016-18).[16]

CLL severely affects quality of life (QoL) in comparison to healthy controls, with factors including higher fatigue, financial difficulties, and anxiety related to health and functional impairment.[17] An international survey of 1,482 patients (2007) showed that emotional QoL was dramatically lower compared to healthy individuals, with contributing factors being older age, greater fatigue, severity of comorbidities and current treatment. In addition to this, QoL scores were significantly lower among individuals with more advanced cancer stage.[18]

Recommended Treatment Options

NICE recommends the following first line treatment options for CLL/SLL:[19]

- Acalabrutinib monotherapy
- Venetoclax with obinutuzumab
- Venetoclax monotherapy
- Ibrutinib monotherapy
- Idelalisib monotherapy
- Idelalisib with rituximab
- Obinutuzumab with chlorambucil
- Bendamustine monotherapy
- Rituximab with fludarabine and cyclophosphamide

Clinical Trial Information

Trial	NCT04170283; An Open-label, Multi-center, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients With B-cell Malignancies **Phase III (Expanded Access):** Enrolling by invitation **Location(s):** 1 EU country, United Kingdom, United States, Australia, China and South Korea **Primary completion date:** December 2024
Trial Design	Non-randomised, open label, single group assignment.
Population	N=500 (estimated); aged 18 years and older; B-cell malignancies
Intervention(s)	• Experimental: Zanubrutinib 160mg zanubrutinib oral capsule twice daily (for a total daily dose of 320mg), or last dose level received in the BeiGene parent study.
Comparator(s)	N/A.
Outcome(s)	Incidence of Adverse Events (AEs) [Time frame: Up to 5 years] Safety as assessed by incidence of all treatment-emergent adverse events (TEAEs) and serious AEs (SAEs) See trial record for a full list of other outcomes

Results (efficacy)	-
Results (safety)	-

Trial	**SEQUOIA; NCT03336333; 2017-001551-31;** An International, Phase 3, Open-Label, Randomized Study of BGB-3111 Compared With Bendamustine Plus Rituximab in Patients With Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma **Phase III** – Recruiting **Location(s):** 8 EU countries, United Kingdom, United States, and other countries **Primary completion date:** January 2022
Trial Design	Randomised, open label, parallel assignment
Population	N=710 (estimated); aged 18 years and older; previously untreated CLL or SLL
Intervention(s)	• Experimental, pivotal randomised: Cohort 1, Arm A: Zanubrutinib Zanubrutinib administered as two 80mg oral capsules twice a day (160mg twice a day). • Experimental, pivotal randomised: Cohort 1, Arm B: Bendamustine and rituximab Bendamustine administered intravenously (IV) at a dose of 90mg/m^2/day on the first 2 days of each cycle for 6 cycles. Rituximab administered IV at a dose of 375mg/m^2 on day 0 of cycle 1, and at a dose of 500mg/m^2 on day 1 of cycles 2 to 6. • Experimental, non-randomised exploratory: Cohort 2, Arm C: Zanubrutinib Zanubrutinib administered as two 80mg capsules by mouth twice a day (160mg twice a day) • Experimental, non-randomised exploratory: Cohort 3, Arm D: Venetoclax + zanubrutinib Zanubrutinib administered as two 80mg capsules by mouth twice a day (160mg twice a day)
Comparator(s)	Bendamustine and rituximab.
Outcome(s)	Cohort 1: Progression-free survival (PFS) between treatment groups (zanubrutinib vs. bendamustine and rituximab) as determined by independent central review (ICR). [Time frame: Up to 5 years] See trial record for a full list of other outcomes
Results (efficacy)	The overall response rate was 94.5% with 3.7% of patients achieving complete response with or without incomplete hematologic recovery. The estimated 18-month progression-free survival rate was 88.6% (95% CI: 79.0–94.0) and the estimated 18-month overall survival rate was 95.1% (95% CI: 88.4–98.0).[6]

Results (safety)	Most common all-grade adverse events included contusion (20.2%), upper respiratory tract infection (19.3%), neutropenia/ neutrophil count decreased (17.4%), and diarrhoea (16.5%). Grade ≥3 adverse events were reported in 53 patients (48.6%), most commonly neutropenia (12.9%) and pneumonia (3.7%). An adverse event of atrial fibrillation was reported in three patients (2.8%).[6]

Trial	NCT02343120; 2016-003364-39; A Phase I/II, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Subjects With B-Cell Lymphoid Malignancies **Phase I/II** – Completed **Location(s):** 1 EU country, United Kingdom, United States, Australia, New Zealand and Republic of Korea **Primary completion date:** March 2021
Trial Design	Open label single group assignment.
Population	N=397 (actual); aged 18 years and older; B-lymphoid malignancies
Intervention(s)	• Experimental: Zanubrutinib 160mg zanubrutinib oral capsule twice daily • 3 + 3 dose escalation: 40, 80, 160, or 320mg oral capsule once daily
Comparator(s)	N/A.
Outcome(s)	Number of participants with adverse events [Time Frame: From first dose to within 28 days of last dose of BGB-3111] Creating a safety profile See trial record for a full list of other outcomes
Results (efficacy)	Median BTK occupancy in peripheral blood mononuclear cells was >95% at all doses. Sustained complete (>95%) BTK occupancy in lymph node biopsy specimens was more frequent with 160 mg twice daily than 320 mg once daily (89% vs 50%; P = .0342). Consequently, 160 mg twice daily was selected for further investigation. Among 78 efficacy-evaluable CLL/SLL patients, the overall response rate was 96.2% (95% confidence interval, 89.2-99.2). Estimated progression-free survival at 12 months was 100%.[20]
Results (safety)	With median follow-up of 13.7 months (range, 0.4-30.5 months), 89 CLL/SLL patients (94.7%) remain on study. Most toxicities were grade 1/2; neutropenia was the only grade 3/4 toxicity observed in >2 patients. One patient experienced a grade 3 subcutaneous hemorrhage.[20]

Estimated Cost

The cost of zanubrutinib was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE Technology Appraisal Guidance awaiting development. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma (ID3860). Expected publication date: March 2023.
- NICE Technology Appraisal Guidance. Acalabrutinib for treating chronic lymphocytic leukaemia (TA689). April 2021.
- NICE Technology Appraisal Guidance. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (TA663). December 2020.
- NICE Technology Appraisal Guidance. Venetoclax for treating chronic lymphocytic leukaemia (TA487). November 2017.
- NICE Technology Appraisal Guidance. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (TA429). January 2017.
- NICE Technology Appraisal Guidance. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015.
- NICE Technology Appraisal Guidance. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343). June 2015.
- NICE Technology Appraisal Guidance. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (TA216). February 2011.
- NICE Technology Appraisal Guidance. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (TA174). July 2009.
- NICE Technology Appraisal Guidance. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (TA119). February 2007.

NHS England (Policy/Commissioning) Guidance

- NHS Northern Cancer Alliance. Haematology Cancer Clinical Guidelines. November 2019.

Other Guidance

- European Society for Medical Oncology (ESMO). Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. October 2020.[21]
- British Committee for Standards in Haematology. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. October 2012.[22]

Additional Information

BeiGene Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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