

## Health Technology Briefing January 2022

### Zanubrutinib for relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma

Company/Developer

BeiGene UK Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 26765

NICE ID: 10748

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. Relapsed cancer is when the cancer returns after treatment, whereas refractory is when the cancer does not respond to treatment. 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 patients with relapsed or refractory CLL/SLL. Relapsed is when the cancer returns after treatment and refractory is when the cancer does not respond to initial treatment. 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 treatment option for patients with relapsed or refractory CLL/SLL that is well tolerated.

#### Proposed Indication

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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Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).<sup>1</sup>

## Technology

### Description

Zanubrutinib (Brukinsa, BGB-3111) is a potent and highly selective small molecule Bruton's tyrosine kinase (BTK) inhibitor.<sup>2</sup> 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).<sup>2,3</sup>

Zanubrutinib is in phase III clinical development (NCT03734016; ALPINE, NCT04170283) for relapsed or refractory CLL/SLL. It is given as 160mg twice daily.<sup>1,4</sup> The recommended total daily dose of zanubrutinib is 320 mg. The daily dose may be taken either once daily (four 80mg capsules) or divided into two doses of 160 mg twice daily (two 80mg capsules).<sup>5</sup>

### Key Innovation

Currently available targeted therapies for patients with CLL/SLL are designed to inhibit intracellular signalling pathways, including the B-cell receptor (BCR), that are associated with the disease. However, these existing targeted therapies also inhibit off-target tyrosine kinases causing toxicities. Therefore, there is an unmet need to develop more effective, and better tolerated treatment options to improve long-term outcomes for patients. In an interim analysis of phase III clinical study (ALPINE, NCT03734016) zanubrutinib showed both efficacy and safety advantages in comparison to ibrutinib, as well as improving outcomes.<sup>6</sup>

### Regulatory & Development Status

Zanubrutinib has EMA and MHRA Marketing Authorisation 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.<sup>7,8</sup>

Zanubrutinib is in phase III/II clinical development for mantle cell lymphoma, marginal zone lymphoma, and lupus nephritis, amongst others.<sup>9</sup>

## 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.<sup>10,11</sup> Small lymphocytic lymphoma (SLL) is considered the same condition as CLL, as most CLL/SLL patients have abnormal lymphocytes in locations that overlap between the two conditions, including lymph nodes, spleen, blood and bone marrow.<sup>12</sup> Risk factors include increased age, being male, having a close relative with CLL, and European descent.<sup>13</sup> Relapsed cancer is when it returns after initial improvement, whereas refractory cancer is cancer that does not respond to treatment.<sup>14,15</sup>

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

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. The most common symptoms include fatigue, pain, insomnia, and appetite loss.<sup>18</sup> 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.<sup>19</sup>

### Recommended Treatment Options

NICE recommends the following treatments for relapsed or refractory CLL/SLL:<sup>20</sup>

- Acalabrutinib monotherapy
- Venetoclax with rituximab
- Venetoclax monotherapy
- Ibrutinib monotherapy
- Idelalisib with rituximab
- Rituximab in combination with fludarabine and cyclophosphamide
- Fludarabine monotherapy

### Clinical Trial Information

Trial	<p><a href="#">NCT04170283</a>; An Open-label, Multi-center, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients With B-cell Malignancies  <b>Phase III (Expanded Access)</b> – Enrolling by invitation  <b>Location(s)</b>: 1 EU country, United Kingdom, United States, Australia, China and South Korea  <b>Primary completion date</b>: December 2024</p>
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	<p><b>ALPINE</b>; <a href="#">NCT03734016</a>; <a href="#">2018-001366-42</a>; A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared With Ibrutinib in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma  <b>Phase III</b> – Active, not recruiting  <b>Location(s)</b>: 9 EU countries, United Kingdom, United States and other countries  <b>Primary completion date</b>: January 2023</p>
Trial Design	Randomised, open label, parallel assignment
Population	N=652 (actual); aged 18 years and older; relapsed or refractory CLL or SLL
Intervention(s)	Zanubrutinib 160mg orally twice daily.
Comparator(s)	Active comparator ibrutinib 420mg orally once daily.
Outcome(s)	<p>Overall response rate (ORR) determined by investigator assessment [Time frame: Up to 50 months]</p> <p>See trial record for a full list of other outcomes</p>
Results (efficacy)	At a median follow-up of 415 patients at 15 months, ORR was significantly higher with zanubrutinib vs ibrutinib (78.3% vs 62.5%, 2-sided P=0.0006 compared with pre-specified alpha of 0.0099 for interim analysis). ORR was higher in patients with del11q (83.6% vs 69.1%) and del17p (83.3% vs 53.8%) with zanubrutinib, as were overall 12-months PFS (94.9% vs 84.0%, Figure) and OS rates (97.0% vs 92.7%). <sup>6</sup>
Results (safety)	The rate of atrial fibrillation/flutter, a pre-specified safety endpoint, was significantly lower with zanubrutinib vs ibrutinib (2.5% vs 10.1%, 2-sided P=0.0014, compared with pre-specified alpha of 0.0099 for interim analysis). Rates of major bleeding (2.9% vs 3.9%), and adverse events leading to discontinuation (7.8% vs 13.0%) or death (3.9% vs 5.8%) were also lower with zanubrutinib. Rate of neutropenia was higher with zanubrutinib (28.4% vs 21.7%), while grade ≥3 infections were lower with zanubrutinib (12.7% vs 17.9%). <sup>6</sup>

Trial	<p><a href="#">NCT02343120</a>; <a href="#">2016-003364-39</a>; 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  <b>Phase I/II</b> – Completed  <b>Location(s)</b>: 1 EU country, United Kingdom, United States, Australia, New Zealand and Republic of Korea  <b>Primary completion date</b>: March 2021</p>
Trial Design	Open label single group assignment.
Population	N=397 (actual); aged 18 years and older; B-lymphoid malignancies
Intervention(s)	<ul style="list-style-type: none"> <li>Experimental: Zanubrutinib 160mg zanubrutinib oral capsule twice daily</li> </ul>

	<ul style="list-style-type: none"> <li>3 + 3 dose escalation: 40, 80, 160, or 320mg oral capsule once daily</li> </ul>
Comparator(s)	N/A.
Outcome(s)	<p>Number of participants with adverse events [ Time Frame: From first dose to within 28 days of last dose of BGB-3111 ]</p> <p>Creating a safety profile</p> <p>See trial record for a full list of other outcomes</p>
Results (efficacy)	<p>Median BTK occupancy in peripheral blood mononuclear cells was &gt;95% at all doses. Sustained complete (&gt;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%.<sup>21</sup></p>
Results (safety)	<p>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 &gt;2 patients. One patient experienced a grade 3 subcutaneous hemorrhage.<sup>21</sup></p>

### Estimated Cost

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

### Relevant Guidance

#### NICE Guidance

- NICE Technology Appraisal Guidance. Acalabrutinib for treating chronic lymphocytic leukaemia (TA689). April 2021.
- NICE Technology Appraisal Guidance. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (TA561). February 2019.
- 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. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (TA193). July 2010.
- NICE Technology Appraisal Guidance. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (TA29). September 2001.

#### 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.<sup>22</sup>
- British Committee for Standards in Haematology. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. October 2012.<sup>23</sup>

### 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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