ALPINE
Clinical Trial Fact Sheet

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Disclaimer: Any information on the products or the CLL disease contained herein is not intended to provide medical advice, and/or treatment guidance. The information within is not intended for promotional purposes.

BRUKINSA is not authorized in all countries for the treatment of CLL; HCPs should consult the approved prescribing information in their respective countries.

The ALPINE Clinical Trial is a global pivotal study designed to evaluate the superiority of BRUKINSA® (zanubrutinib) vs ibrutinib in previously treated (second-line) patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who received at least 1 prior systemic therapy.[1,2]

In the final analysis of the ALPINE trial, where progression-free survival (PFS) was a key secondary endpoint, BRUKINSA demonstrated superior efficacy and a favorable cardiac safety profile vs. IMBRUVICA in R/R CLL patients, which was presented in a late-breaking session at the 64th American Society of Hematology Annual Meeting. These results were published simultaneously in The New England Journal of Medicine. A previous final analysis also demonstrated superiority in overall response rate (ORR).[8]

A slow-growing, life-threatening, and incurable cancer of older adults, CLL is the most common leukemia in adults.[3-6] CLL and SLL are considered different manifestations of the same disease.[7]

THE ALPINE CLINICAL TRIAL (NCT03734016)[1,2]

Trial Design

- Randomized, global Phase 3 trial–the **largest head-to-head study of BTK inhibitors in R/R CLL**
- Enrolled 652 patients across Europe (60%), the United States (17%), China (14%), New Zealand, and Australia (9%)

Key Inclusion Criteria:

- R/R with more than 1 prior systemic therapy
- Measurable lymphadenopathy (by CT or MRI)

Key Exclusion Criteria:

- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or vitamin K antagonists

The ALPINE Trial consisted of 2 arms and enrolled 324 patients in each:

Arm 1: 160 mg BRUKINSA twice daily

Arm 2: 420 mg ibrutinib once daily

Key Endpoints

Primary endpoint:

Overall response rate (ORR), defined by prespecified noninferiority of BRUKINSA vs ibrutinib, as assessed by investigator and the Independent Review Committee (IRC) using the 2008 International Workshop on CLL guidelines.

Note: There was hierarchical testing of noninferiority followed by superiority in ORR as assessed by investigator and the IRC.[1]

Key secondary endpoints:

- Investigator-assessed progression-free survival
- Event rate of atrial fibrillation or flutter
- Duration of response
- Overall survival
- Adverse event

*BRUKINSA has been approved in the United States for the treatment of adults with CLL, WM, MZL, and MCL. BRUKINSA and BeiGene are registered trademarks owned by Beigene, Ltd.

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Trial Results:

At the final analysis (n=652), BRUKINSA® (zanubrutinib) met its primary endpoint, demonstrating superiority in investigator-assessed ORR compared to ibrutinib, with a median follow up of 29.6 months.[8]

Key Efficacy Findings[8]	**ORR** BRUKINSA: 86.2% Ibrutinib: 75.7% (two-sided p=0.0264)	**Superior PFS** HR: 0.65 [95% CI, 0.49-0.86] p=0.0024	**Estimated 24 mo PFS** BRUKINSA: 78.4% Ibrutinib: 65.9% (HR: 0.52; [95% CI, 0.30-0.88])
Key Safety Findings[8]	• Safety profile of BRUKINSA was consistent with prior studies and uniform between indications and treatment groups • Median duration of treatment was 28.4 months [0.4-41.6] in the BRUKINSA group and 24.3 months [0.1-45.1] in the ibrutinib group • Incidence of atrial fibrillaton or flutter of any grade was lower with BRUKINSA vs. ibrutinib (5.2% vs. 13.3%) • BRUKINSA demonstrated tolerability **with lower discontinuation rates** vs ibrutinib (15.4% vs. 22.2%)		
Most Commonly Reported Grade ≥3 or Higher AEs[8]	**BRUKINSA vs ibrutinib** • **Pneumonia** (5.9% vs. 8.0%) • **Anemia** (2.2% vs. 2.5%) • **Blood pressure increased** (1.2% vs. 3.1%)		

About BRUKINSA:

BRUKINSA is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK) discovered by BeiGene scientists that is currently being evaluated globally in a broad clinical program as a monotherapy and in combination with other therapies to treat various B-cell malignancies. BRUKINSA was specifically designed to deliver targeted and sustained inhibition of the BTK protein by optimizing bioavailability, half-life, and selectivity. With differentiated pharmacokinetics compared to other approved BTK inhibitors, BRUKINSA has been demonstrated to inhibit the proliferation of malignant B cells within a number of disease-relevant tissues.

BRUKINSA is supported by a broad clinical program which includes more than 4,700 subjects in 35 trials in more than 25 countries and regions. To date, BRUKINSA is approved in over 60 markets, including the United States, China, the European Union Great Britain, Canada, Australia, South Korea, Switzerland and additional international markets.

The full prescribing information can be found at: https://www.brukinsa.com/prescribing-information.pdf

References:

1. IRC determines BRUKINSA® (zanubrutinib) demonstrates superior overall response rate versus ibrutinib in final response analysis of ALPINE Trial in chronic lymphocytic leukemia. BeiGene Company Press Release. Accessed April 11, 2022. https://www.businesswire.com/news/home/20220411005299/en/IRC-Determines-BRUKINSA%C2%AE-Zanubrutinib-Demonstrates-Sperior-Overall-Response-Rate-Versus-Ibrutinib-in-Final-Response-Analysis-of-ALPINE-Trial-in-Chronic-Lymphocytic-Leukemia

2. A study of zanubrutinib (BGB-3111) versus ibrutinib in participants with relapsed/refractory chronic lymphocytic leukemia. ClinicalTrials.gov. Accessed September 25, 2022. https://clinicaltrials.gov/ct2/show/NCT03734016

3. Surveillance, epidemiology, and end results program. Cancer Stat Facts: Leukemia—chronic lymphocytic leukemia (CLL). Accessed October 4, 2021. https://seer.cancer.gov/statfacts/html/clyl.html

4. Aster JC, Freedman A. Non-hodgkin lymphomas and chronic lymphocytic leukemias. In: Aster JC, Bunn HF, eds. *Pathophysiology of Blood Disorders.* 2nd ed. McGraw-Hill Education; 2017:chap 22.

5. What is chronic lymphocytic leukemia? American Cancer Society. Updated May 10, 2018. Accessed December 6, 2020. https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html

6. Yao Y, Lin X, Li F, Jin J, Wang H. The global burden and attributable risk factors of chronic lymphocytic leukemia in 204 countries and territories from 1990 to 2019: analysis based on the global burden of disease study 2019. *BioMed Eng OnLine.* 2022;21(1):4. doi:10.1186/s12938-021-00973-6

7. National Comprehensive Cancer Network. chronic lymphocytic leukemia/small lymphocytic lymphoma. December 3, 2020.

8. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. doi:10.1056/NEJMoa2211582.

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