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Nemtabrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Cohort J of the Phase 2 BELLWAVE-003 Study

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Background

- Treatment options for patients with relapsed or refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) are limited if patients do not respond to Bruton tyrosine kinase inhibitors (BTKis) and B-cell lymphoma 2 inhibitors (BCL2is)[1]
- Nemtabrutinib is a once-daily (QD), potent, noncovalent, competitive, reversible BTKi with a distinct kinase profile, inhibiting BTK and other B-cell receptor–relevant kinases[2,3]
  - Nemtabrutinib does not require the C481 residue of BTK for the binding and inhibition of kinase activity; as a result, nemtabrutinib can target both the wild type and the C481-mutant forms of BTK
- Nemtabrutinib has additional activity against Src family kinases and kinases related to ERK signaling, which may produce more robust responses.[2] In vitro studies also showed a lack of mutation in *BTK* and *PLCG2* domains through targeted next-generation sequencing in cell lines treated with nemtabrutinib, which contrasts with other noncovalent BTKis.[4] Nemtabrutinib also showed preclinical efficacy in cell lines carrying mutations derived from participants treated with pirtobrutinib[5]
- In the multicenter, open-label, single-arm, phase 2 BELLWAVE-003 study (NCT04728893), we are evaluating nemtabrutinib in participants with R/R CLL/SLL, Richter transformation, mantle cell lymphoma, marginal zone lymphoma, follicular lymphoma, and Waldenström macroglobulinemia across 9 cohorts [6,7]
  - This study comprises a dose escalation and confirmation phase in which we previously established the recommended phase 2 dose (RP2D) as nemtabrutinib 65 mg by mouth (PO) QD, and a cohort expansion phase in which we are evaluating nemtabrutinib at the RP2D
- In cohort J, we will evaluate nemtabrutinib in participants with R/R CLL/SLL who are R/R to both a BTKi (covalent and/or noncovalent) and a BCL2i. Prior treatment with a noncovalent BTKi is permitted if the participant experienced relapse or disease progression, allowing the possible assessment of the clinical activity of nemtabrutinib after other noncovalent BTKis

Objectives

Primary

- To evaluate objective response rate (ORR) per International Workshop on CLL (iwCLL) 2018 criteria by independent central review (ICR) (complete response [CR] or CR with incomplete bone marrow recovery or partial response [PR] or nodular PR)

Secondary

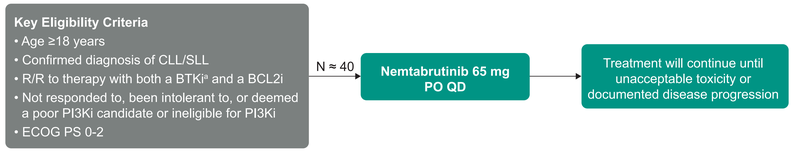
- To evaluate the following:
  - Pharmacokinetics (PK) profile
  - Safety and tolerability
  - Duration of response (DOR) per iwCLL 2018 criteria by ICR

Exploratory

- To evaluate the following:
  - Response category of PR with lymphocytosis per iwCLL 2018 criteria by ICR
  - Minimal residual disease per iwCLL 2018 criteria by ICR
  - Progression-free survival (PFS) per iwCLL 2018 criteria by ICR
  - Overall survival (OS)
  - Changes from baseline in health-related quality of life
- To investigate the relationship between the efficacy outcomes of nemtabrutinib per iwCLL criteria 2018 by ICR and BTK-C481 mutation status
- To identify molecular biomarkers

Methods

Study design: BELLWAVE-003 cohort J



ECOG PS, Eastern Cooperative Oncology Group performance status; PI3Ki, phosphoinositide 3-kinase inhibitor.
[a]Additional use of noncovalent or reversible BTKis is permitted if disease is R/R to such therapy.

Participant eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Confirmed CLL/SLL • R/R to prior therapy with a covalent/irreversible BTKi and a BCL2i (both classes are required) – Additional use of noncovalent or reversible BTKis is permitted if disease is R/R to such therapy • Have not responded to, been intolerant to, or been determined by treating physician to be a poor PI3Ki candidate or ineligible to receive a PI3Ki per local (institution) guidelines • ECOG PS score of 0 to 2 within 7 days before allocation • Life expectancy of ≥3 months • Adequate organ function	• Active hepatitis B virus or hepatitis C virus infection • History of malignancy ≤3 years before allocation • Active central nervous system disease • Active infection necessitating systemic therapy • Prior systemic therapy within 5 half-lives or 4 weeks before allocation • Currently participating in or has participated in a study of an investigational agent within 4 weeks before the first dose of study drug • Known severe hypersensitivity (grade ≥3) to nemtabrutinib, its active substance, or any of its excipients • History of severe bleeding disorders • Clinically significant gastrointestinal abnormalities that might alter absorption

Assessments and follow-up

Assessment	Detail
AEs	• AEs will be monitored and assessed by investigators throughout the study and for 30 days after the last dose of study drug (90 days for serious AEs, or 30 days if new anticancer therapy is initiated, whichever is earlier) • AEs will be graded per NCI Common Terminology Criteria for Adverse Events, version 5.0 • Hematologic toxicity will be assessed using iwCLL 2018 criteria
Response	• CT/MRI or PET imaging will be performed every 12 weeks, unless needed more frequently
PROs	• PRO questionnaires will be administered before all other study procedures and before receiving results of any tests (including disease status)

AE, adverse event; CT, computed tomography; MRI, magnetic resonance imaging; NCI, National Cancer Institute; PET, positron emission tomography; PRO, patient-reported outcome.

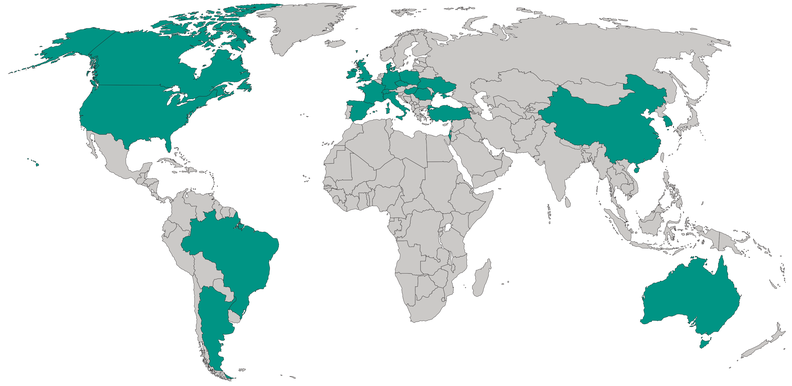
Analyses

Analysis	Detail
Efficacy	• Efficacy analysis will be conducted in the APaT population, which will consist of all participants who receive ≥1 dose of study drug • ORR and its 95% CI will be estimated using the exact binomial method • DOR, PFS, and OS will be estimated using the Kaplan-Meier method
Safety	• Safety analysis will be conducted in the APaT population, which will consist of all participants who receive ≥1 dose of study drug • Safety will be summarized descriptively
PK	• PK analysis will be conducted in the APaT population • PK parameters, including AUC, C_{max}, and C_{min}, will be summarized by planned visit and time for each dose separately
PROs	• PROs will be assessed in the PRO FAS population, defined as all allocated participants who have both baseline and ≥1 postbaseline assessment and have received ≥1 dose of study treatment

APaT, all-participants-as-treated; AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; FAS, full analysis set.

Status

Sites of participant enrollment for BELLWAVE-003 (green)



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Acknowledgments

The authors thank the participants and their families and caregivers for their involvement in this trial, as well as all investigators and site personnel. Medical writing and/or editorial assistance was provided by Bresler Swanepoel, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Presented at the 2025 ASCO Annual Meeting; May 30-June 3, 2025 (TPS7088).

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Presented at the XXI International Workshop on Chronic Lymphocytic Leukemia (iwCLL); Kraków, Poland; September 12-15, 2025