FIRST INTERIM ANALYSIS OF ALPINE STUDY: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VS IBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKAEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL)

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ABSTRACT

Introduction: CLL/SLL treatment has been transformed with Bruton tyrosine kinase inhibitors (BTKi) such as ibrutinib. Zanubrutinib, a next-generation BTKi, was designed to maximize BTK occupancy and minimize toxicity. ALPINE (NCT03734016) is a global, randomized, phase 3 study of zanubrutinib vs ibrutinib in patients with R/R CLL/SLL; presented here is a preplanned interim analysis conducted ~12 months after enrollment of 415 patients.

Methods: Patients were randomized 1:1 to receive zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily); stratification factors included age (<65 years vs ≥65 years), geographic region, refractory status, and del(17p)/*TP53* mutation. The primary endpoint was overall response rate (ORR) per 2008 IWCLL guidelines or Lugano criteria as assessed by the investigator. Noninferiority of the zanubrutinib-to-ibrutinib response ratio was evaluated at a noninferiority margin of 0.8558; if noninferiority was demonstrated, superiority of zanubrutinib vs ibrutinib in ORR was tested.

Results: Of the 415 patients enrolled between 5Nov2018 and 20Dec2019, 30 were enrolled across 10 different sites in Spain. Baseline characteristics for the zanubrutinib vs ibrutinib arms were: age ≥65 years: 62.3% vs 61.5%; male sex: 68.6% vs 75%; >3 prior therapies: 7.2% vs 10.1%; del(17p): 11.6% vs 12.5%; *TP53* mutation without del(17p): 8.2% vs 5.8%. With a median follow-up of 15 months, ORR was 78.3% vs 62.5% for zanubrutinib vs ibrutinib (2-sided *P*=.0006, prespecified α=0.0099). ORR was higher for zanubrutinib vs ibrutinib in patients with del(11q) (83.6% vs 69.1%) and del(17p) (83.3% vs 53.8%); overall 12-month progression-free survival (PFS; 94.9% vs 84.0%) and overall survival (97.0% vs 92.7%) were also higher with zanubrutinib. Significantly fewer patients had atrial fibrillation/flutter (AF) with zanubrutinib vs ibrutinib (2.5% vs 10.1%, 2-sided *P*=.0014, prespecified α=0.0099). Zanubrutinib had lower rates of major bleeding (2.9% vs 3.9%), adverse events leading to discontinuation (7.8% vs 13.0%), and death (3.9% vs 5.8%). Zanubrutinib had higher neutropenia rate (28.4% vs 21.7%) while grade ≥3 infections (12.7% vs 17.9%) were lower.

Conclusions: This interim analysis showed zanubrutinib had a superior ORR, improved PFS, and lower AF rate compared with ibrutinib.