A Longitudinal Analysis of Patients with CLL/SLL with Impaired Health-Related Quality of Life Scores at Baseline Who Were Treated with Zanubrutinib Versus Ibrutinib: A Post Hoc Analysis of ALPINE

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Background In relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), baseline health-related quality of life (HRQoL) impairment may reflect greater disease burden and heightened vulnerability to treatment-related symptoms. Prior analyses demonstrated a significant progression-free survival (PFS) advantage for zanubrutinib versus ibrutinib regardless of baseline HRQoL impairment, as assessed using the visual analog scale of the EuroQol 5 dimension questionnaire (EQ VAS) (Ysebaert et al. *Blood* 2025).

Aims To evaluate longitudinal patient-reported HRQoL with zanubrutinib versus ibrutinib and assess whether effects differed by baseline HRQoL impairment in patients with CLL/SLL in the Phase 3 ALPINE trial (NCT03734016).

Methods Patients provided informed consent and completed two validated patient-reported outcome (PRO) instruments to assess HRQoL: the EQ VAS and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) fatigue scale. Baseline HRQoL impairment was defined separately using two prespecified clinician-informed thresholds: EQ VAS, <70 (impaired) and ≥70 (not impaired); QLQ-C30 fatigue, >39 (impaired) and ≤39 (not impaired). Lower scores in EQ VAS and higher scores in QLQ-C30 fatigue indicated greater impairment. PROs were analyzed longitudinally using a mixed model for repeated measures (MMRM) with visit (time) treated nominally, incorporating all available post-baseline PRO assessments. Prespecified contrasts evaluated overall treatment effects, treatment-by-impairment differences, and month-specific treatment effects by

impairment status at Months 6 and 12 (treatment × baseline impairment status × month). *P*-values for prespecified contracts were Tukey–Kramer adjusted.

Results Overall, 573 patients were included in the EQ VAS analysis (not impaired n=416; impaired n=157) and 575 in the QLQ-C30 fatigue analysis (not impaired n=365; impaired n=210). In the MMRM, zanubrutinib was associated with significantly better EQ VAS scores versus ibrutinib (−3.52 [95% confidence interval {CI}: −5.58 to −1.46]; *P*=0.0008), regardless of baseline impairment status. Among baseline-impaired patients, the between-group difference in EQ VAS score favored zanubrutinib versus ibrutinib (−6.08 [95% CI: −10.40 to −1.76]; *P*=0.0018). In month-specific contrasts within the impaired subgroup, EQ VAS scores significantly favored zanubrutinib versus ibrutinib at month 6 (−6.73 [95% CI: −12.49 to −0.96]; *P*=0.0098), with a directionally consistent, clinically relevant between-arm difference observed at month 12 (−5.43 [95% CI: −11.21 to 0.35]; *P*=0.0833) (Fig 1). For QLQ-C30 fatigue, no overall or month-specific between-arm differences were observed.

Conclusion Treatment with zanubrutinib resulted in better overall health status (EQ VAS) compared with ibrutinib among patients with baseline HRQoL impairment. Taken together with prior evidence that zanubrutinib provided consistent PFS benefit regardless of baseline HRQoL impairment status, these empirical results identify baseline HRQoL impairment as a critical factor at the time of treatment initiation and may help inform early symptom monitoring and supportive care planning in patients with CLL/SLL.

Fig 1. Treatment × Baseline Impairment Status × Month