Zanubrutinib vs ibrutinib in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL): impact on health-related quality of life (HRQoL)

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Introduction: Zanubrutinib is a potent and highly selective next-generation Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize off-target effects. In the ALPINE study (NCT03734016), zanubrutinib was compared head-to-head with ibrutinib as treatment for R/R CLL/SLL, where it demonstrated superiority to ibrutinib in both progression-free survival and overall response rate and a more favorable safety profile. The purpose of this analysis was to assess HRQoL in patients treated with zanubrutinib and ibrutinib. Results from the data cutoff (8 August 2022) related to recent progression-free survival analysis are reported here.

Methods: HRQoL was measured by EORTC QLQ-C30 and EQ-5D-5L at baseline, Cycle 1, and then every third 28-day cycle until end of treatment. Key patient-reported outcome (PRO) endpoints included global health status (GHS), physical and role functions, fatigue, pain, diarrhea, and nausea/vomiting. Descriptive analysis was conducted on all the scales; a mixed models for repeated measures analysis using key PRO endpoints at the key clinical cycles of Cycles 7 (6 months) and 13 (12 months) was performed. Adjusted completion rates were defined as the number of patients who completed the questionnaires at each cycle divided by the number of patients still on treatment. Clinically meaningful was defined as a ≥5% mean change difference from baseline.

Results: A total of 652 patients were randomized to receive zanubrutinib (n=327) or ibrutinib (n=325); baseline characteristics were generally similar between arms, although the zanubrutinib arm had fewer males than the ibrutinib arm (65.1% vs 71.4%). At baseline, GHS, functional, and symptom scale scores were similar between arms. Although more ibrutinib-treated patients discontinued treatment due to adverse events than zanubrutinib-treated patients (22.2% vs 15.4%), adjusted PRO completion rates were high at Cycles 7 and 13 in both the zanubrutinib arm (89.6% and 94.3%) and ibrutinib arm (87.7% and 92.3%), respectively. By Cycle 7, GHS scores were improved with zanubrutinib vs ibrutinib (least-squares mean change difference, 3.0 [95% CI: 0.23, 5.77]; nominal *P*=.0338). By Cycle 13, the difference in GHS scores from baseline was no longer significant (least-squares mean change difference, 1.34 [95% CI: −1.37, 4.06]; nominal *P*=.3304) (**Table**). Patients in the zanubrutinib arm experienced clinically meaningful improvements in physical and role functioning as well as pain and fatigue at Cycles 7 and 13, but the difference between the arms was not significant. Although patients in the zanubrutinib arm reported lower diarrhea scores, the difference between treatments was not significant. Nausea/vomiting scores were maintained in both arms with no measurable difference. VAS scores

showed greater improvement from baseline at both Cycles 7 (7.92 vs 3.44) and 13 (7.75 vs 3.92) with zanubrutinib vs ibrutinib treatment, respectively.

Conclusions: In ALPINE, patients with R/R CLL/SLL treated with zanubrutinib demonstrated improvement over those treated with ibrutinib in the QLQ-30 GHS/QoL scale at Cycle 7 (6 months). Other endpoints continued to improve, suggesting treatment with zanubrutinib positively affected HRQoL and that HRQoL improved over time. As expected, given the generally good HRQoL at baseline in both arms, the differences between the arms were small and not significant.

Table: Least-Squares Mean Differences (95% CI) From Baseline Within and Between Treatment Arms

	Cycle 7 (6 months)			Cycle 13 (12 months)		
	Zanubrutinib n=327	**Ibrutinib n=325**		**Zanubrutinib n=327**	**Ibrutinib n=325**	
	Difference Within the Arm	Difference Within the Arm	**Difference Between the Arms**	Difference Within the Arm	Difference Within the Arm	**Difference Between the Arms**
Global Health Status	8.18 (6.25, 10.12)	5.18 (3.20, 7.17)	**3.00 (0.23, 5.77)***	7.28 (5.41, 9.15)	5.93 (3.97, 7.89)	1.34 (−1.37, 4.06)
Physical functioning	6.55 (4.96, 8.15)	4.73 (3.08, 6.38)	1.82 (−0.47, 4.12)	5.46 (3.87, 7.04)	4.31 (2.65, 5.97)	1.15 (−1.15, 3.44)
Role functioning	6.95 (4.85, 9.06)	6.32 (4.14, 8.50)	0.63 (−2.40, 3.66)	6.81 (4.61, 9.02)	5.01 (2.69, 7.33)	1.80 (−1.40, 5.00)
Fatigue†	−12.54 (−14.47, −10.60)	−10.63 (−12.63, −8.62)	−1.91 (−4.70, 0.87)	−11.13 (−13.19, −9.08)	−10.78 (−12.93, −8.63)	−0.35 (−3.32, 2.62)
Nausea/vomiting†	−1.21 (−2.03, −0.38)	−0.92 (−1.77, −0.07)	−0.29 (−1.48, 0.89)	−0.92 (−1.94, 0.10)	−0.40 (−1.47, 0.66)	−0.51 (−1.99, 0.96)
Pain†	−5.06 (−7.21, −2.91)	−3.63 (−5.85, −1.42)	−1.43 (−4.51, 1.66)	−5.18 (−7.38, −2.97)	−2.75 (−5.06, −0.44)	−2.43 (−5.62, 0.77)
Diarrhea†	−2.11 (−3.80, −0.42)	−0.52 (−2.27, 1.22)	−1.59 (−4.01, 0.84)	−3.23 (−4.79, −1.66)	−1.38 (−3.03, 0.27)	−1.85 (−4.12, 0.43)

Data cutoff: 8 August 2022.

*Nominal *P*-value <.05.

†Negative values indicate improvement.