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

- Symptoms that patients with chronic lymphocytic leukemia (CLL), including small lymphocytic lymphoma (SLL), may experience have a profound negative impact on patients' health-related quality of life (HRQoL)[1,2]
- The ALPINE trial (NCT03734016), a randomized, open-label, multi-country phase 3 study, compared zanubrutinib with ibrutinib in patients with R/R CLL/SLL.[3] The final PFS analysis (August 8, 2022 cutoff date) showed the following:
  - At a median follow-up of 29.6 months, zanubrutinib demonstrated superior PFS to ibrutinib (HR: 0.65 [95% CI, 0.49–0.86]; 2-sided *P*=.0024) and continued to show an improved overall response rate (86.2% vs 75.7%, nominal 2-sided *P*=.0007)[4]
- The purpose of the current analyses was to assess HRQoL, as a secondary objective, in patients treated with zanubrutinib or ibrutinib in the ALPINE trial

METHODS

- The study population consisted of adult patients (aged ≥18 years) that had a confirmed diagnosis of CLL/SLL that met International Workshop on CLL criteria, were R/R to ≥1 prior systemic therapy, and had an Eastern Cooperative Oncology Group performance status of ≤2
- Eligible patients were randomized 1:1 to receive zanubrutinib (160 mg oral BID, n=327) or ibrutinib (420 mg oral QD, n=325) until PD or unacceptable treatment-related toxicity

HRQoL Assessments and Endpoints

- Key clinical cycles were Cycles 7 and 13
- Key endpoints from the patient-reported outcomes (PROs) were:
  - The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30): global health status (GHS) scale, 2 functional scales (physical functioning and role functioning), and 4 symptom scales (fatigue, pain, nausea/vomiting, and diarrhea)
    - GHS and functioning scales: higher scores indicate better HRQoL; higher scores on the symptom scales suggest worsening HRQoL
  - The European Quality of Life 5-dimension 5-level questionnaire (EQ-5D-5L): a visual analog scale (VAS) for patients to rate their general health "today"

Statistical Analyses

- Changes from baseline for each of the key EORTC QLQ-C30 scales and EQ-5D-5L VAS were analyzed descriptively using means and SDs
- A mixed model for repeated measures (MMRM) compared changes in EORTC QLQ-C30 scores from baseline by treatment group at Cycles 7 and 13
  - MMRM analyses were conducted only for the key PRO endpoints, in accordance with FDA/EMA requirements, and were selected a priori
- Clinically meaningful change was defined as a ≥5-point mean difference from baseline

RESULTS

Patient Demographic and Clinical Characteristics

- The ITT population consisted of a total of 652 patients (zanubrutinib=327 patients; ibrutinib=325 patients)
- Patient demographics and baseline characteristics were comparable in the zanubrutinib and ibrutinib treatment arms (**Table 1**)
- The observed means and mean change from baseline for the EORTC QLQ-C30 are provided in **Supplemental Table 1**, available for download by scanning the following Quick Response (QR) code at right

Table 1. Patient Demographics and Disease Characteristics

	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range)	67 (35–90)	68 (35–89)
≥65 years, n (%)	201 (61.5)	200 (61.5)
Male, n (%)	213 (65.1)	232 (71.4)
ECOG PS ≥1, n (%)	198 (60.6)	203 (62.5)
Prior lines of systemic therapy, median (range)	1 (1–6)	1 (1–12)
>3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and/or *TP53*mut, n (%)	75 (22.9)	75 (23.1)
del(17p)	45 (13.8)	50 (15.4)
*TP53*mut without del(17p)	30 (9.2)	25 (7.7)
del(11q), n (%)	91 (27.8)	88 (27.1)
IGHV mutational status, n (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	239 (73.1)	239 (73.5)
Complex karyotype[a]	56 (17.1)	70 (21.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

[a]Complex karyotype is defined as having ≥3 abnormalities.
ECOG PS, Eastern Cooperative Oncology Group performance status.

Adjusted Completion Rates

- The adjusted completion rates were high (>87%) in both treatment groups at each assessment timepoint (**Table 2**)

Table 2. Adjusted Completion Rates for HRQoL Assessments

		Zanubrutinib (n=327)	Ibrutinib (n=325)
Baseline	Number of patients	327	325
	Number of completed questionnaires	315	312
	Completion rate n (%)[a]	315 (96.3)	312 (96.0)
	Adjusted completion rate n (%)[b]	315 (96.3)	312 (96.0)
Cycle 7	Number of patients	307	292
	Number of completed questionnaires	275	256
	Completion rate n (%)[a]	275 (84.1)	256 (78.8)
	Adjusted completion rate n (%)[b]	275 (89.6)	256 (87.7)
Cycle 13	Number of patients	296	271
	Number of completed questionnaires	279	250
	Completion rate n (%)[a]	279 (85.3)	250 (76.9)
	Adjusted completion rate n (%)[b]	279 (94.3)	250 (92.3)

[a]Completion rate: number of patients completed questionnaire/total number of patients in relevant treatment arm.
[b]Adjusted completion rate: number of patients completed questionnaire/total number of patients in study at relevant visits in relevant treatment arm.
HRQoL, health-related quality of life.

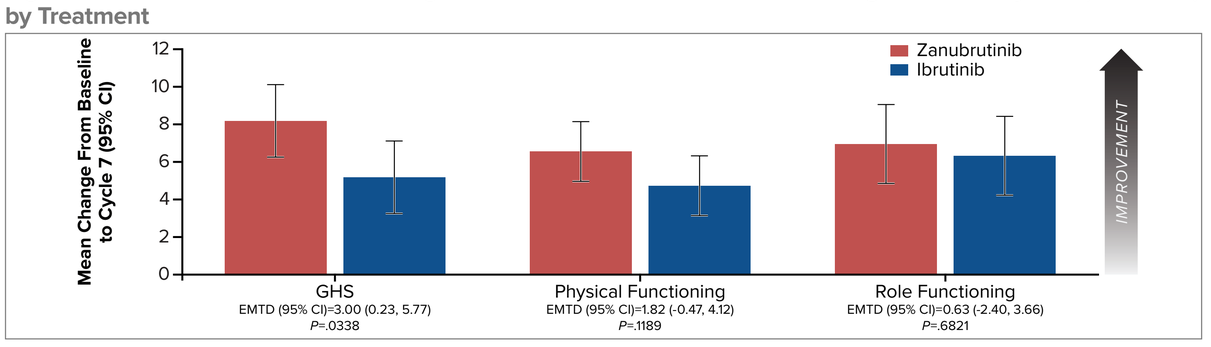
Change From Baseline for EORTC QLQ-C30 in GHS and Functioning Scales

- Both arms improved from baseline to both Cycle 7 (**Figure 1**) and Cycle 13 (**Figure 2**)
- All improvements were clinically meaningful for the zanubrutinib arm; however, by Cycle 13, no clinically meaningful differences were observed between the 2 treatment arms

CONCLUSIONS

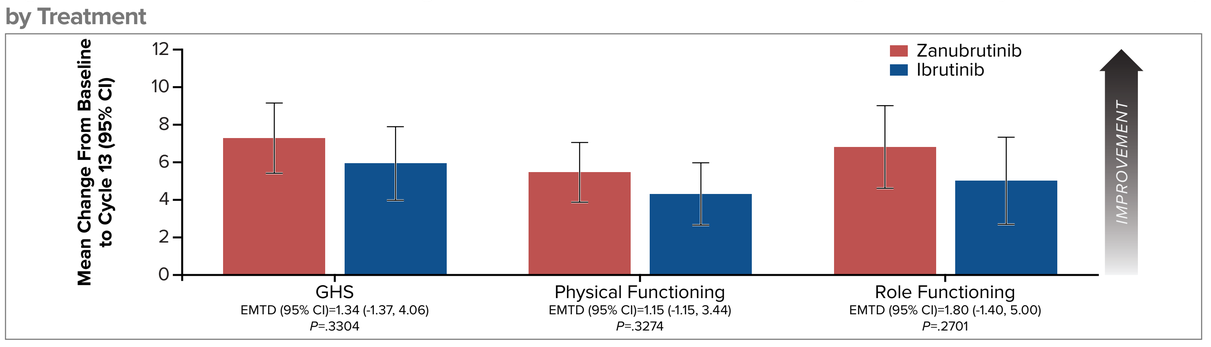
- The results of this study suggest that zanubrutinib monotherapy improves HRQoL outcomes in patients with R/R CLL/SLL
- These improvements were maintained from 6 months through 12 months, the cutoff point for these analyses, suggesting treatment with zanubrutinib positively affected and improved HRQoL over time
- Given the generally good HRQoL at baseline in both arms, the differences between the arms were not significant
- Long-term follow-up as well as additional analyses linking PRO endpoints to clinical outcomes will further determine the full extent to which zanubrutinib improves patient HRQoL

Figure 1. EORTC QLQ-C30 Mean Change From Baseline in GHS and Functioning Scales[a] at Cycle 7 (6 Months) by Treatment



[a]The observed means and mean change from baseline for the QLQ-C30 are provided in **Supplemental Table 1**.
EMTD, estimated mean treatment difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; GHS, global health status.

Figure 2. EORTC QLQ-C30 Mean Change From Baseline in GHS and Functioning Scales[a] at Cycle 13 (12 Months) by Treatment



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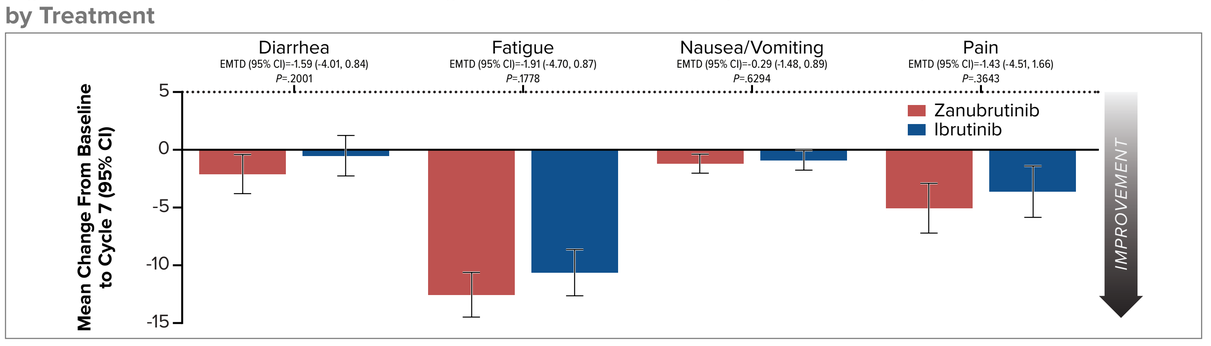
Change From Baseline for EORTC QLQ-C30 in Symptom Scales

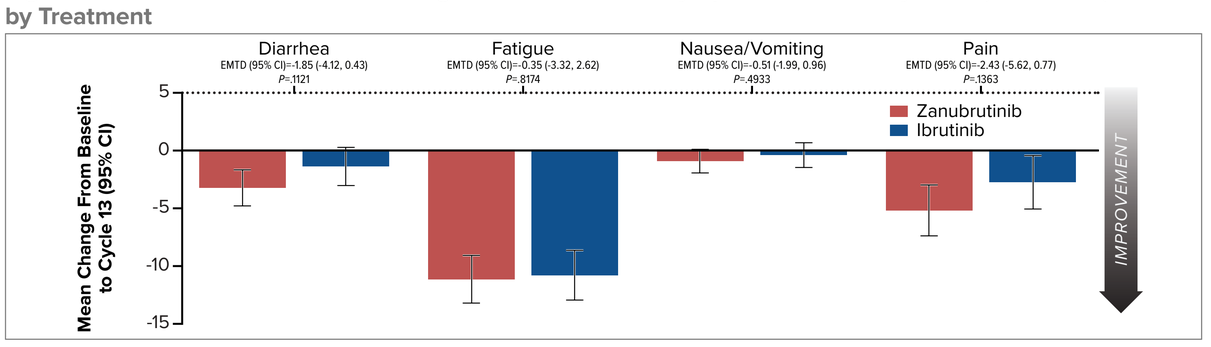
- Both arms experienced a decrease in fatigue and pain, with the zanubrutinib arm experiencing clinically meaningful improvements in both symptoms at both cycles (**Figure 3** and **Figure 4**)
- Higher improvement was observed for diarrhea in the zanubrutinib arm, but the improvement did not reach the predefined clinically meaningful threshold

Figure 3. EORTC QLQ-C30 Mean Change From Baseline in Symptom Scales at Cycle 7 (6 Months) by Treatment



EMTD, estimated mean treatment difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30.

Figure 4. EORTC QLQ-C30 Mean Change From Baseline in Symptom Scales at Cycle 13 (12 Months) by Treatment



EMTD, estimated mean treatment difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30.

EQ-5D-5L VAS

- At baseline, the EQ-5D-5L VAS scores were similar between treatment arms (mean [SD]: 70.79 [19.40] for zanubrutinib and 72.59 [17.38] for ibrutinib)
- The mean change from baseline in the EQ-5D-5L VAS demonstrated a similar pattern of improvement with zanubrutinib and ibrutinib therapy up to Cycle 13
- At Cycle 7, the mean change (SD) from baseline was 7.92 (18.25) and 3.44 (16.97) for zanubrutinib and ibrutinib, respectively
- At Cycle 13, the mean change (SD) from baseline was 7.75 (18.81) for zanubrutinib compared to 3.92 (16.78) for ibrutinib

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DISCLOSURES

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