Zanubrutinib demonstrates superior progression-free survival (PFS) vs ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL): final analysis of randomized phase 3 ALPINE study

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Aim: Zanubrutinib, a more selective, next-generation Bruton tyrosine kinase inhibitor (BTKi) with improved BTK occupancy across disease-relevant tissues, was shown to be superior to the first-generation BTKi, ibrutinib, in the primary endpoint of overall response rate (ORR) by both independent review committee (IRC) and investigator in the predefined interim analysis of

the phase 3 ALPINE trial (NCT03734016). Here, data from the predefined final analysis of the key secondary efficacy endpoint of PFS are reported.

Method: In ALPINE, patients with R/R CLL/SLL who received ≥1 prior therapy and had measurable disease were randomized 1:1 to receive zanubrutinib (n=327) or ibrutinib (n=325) until disease progression or unacceptable toxicity. As zanubrutinib was assessed as superior to ibrutinib in predefined interim analysis of the ORR primary endpoint, the key secondary efficacy endpoint, PFS, was assessed by hierarchical testing after 205 PFS events were reached. If zanubrutinib noninferiority was shown, superiority of zanubrutinib over ibrutinib could be tested and supported at a 2-sided *P* value of <.04996. Other endpoints included overall survival (OS) and safety.

Results: At data cutoff (August 8, 2022; median follow-up, 29.6 months), PFS per IRC was superior with zanubrutinib vs ibrutinib in the intention-to-treat population (hazard ratio, 0.65; *P*=.0024) (**Table**). Across major predefined subgroups, PFS by IRC and investigator consistently favored zanubrutinib over ibrutinib, including in patients with *del(17p)/TP53* mutation. The hazard ratio for OS with zanubrutinib vs ibrutinib was 0.76 (95% CI, 0.51-1.11). For multiple safety variables, rates were lower with zanubrutinib than with ibrutinib (**Table**).

Conclusion: ALPINE is the first study to show PFS superiority with zanubrutinib in a head-to-head comparison of BTKis in patients with R/R CLL/SLL. These data, with those from the predefined interim analysis, show that zanubrutinib had superior ORR and PFS and a favorable safety profile vs ibrutinib in patients with R/R CLL/SLL.

Table. PFS and Safety Results

	Zanubrutinib	Ibrutinib	Hazard ratio (95% CI)
PFS[a] in intention-to-treat population[b]			
Events, n (%)	88 (26.9)	120 (36.9)	0.65 (0.49-0.86); *P*=.0024[c]
Median (95% CI), months	Not reached	35.0 (33.2-44.3)	-
Rate at 24 months, %	79.5	67.3	-
PFS[a] in patients with *del17p/TP53* mutation[d]			
Events, n (%)	23 (30.7)	34 (45.3)	0.52 (0.30-0.88); *P*=.0134[e]
Rate at 24 months, %	77.6	55.7	-
Overall treatment discontinuation, %	26.3	41.2	-
Treatment discontinuation due to cardiac disorders, %	0.3	4.3	-
Grade 5 AEs due to cardiac disorders, %	0.0	1.9	-
Grade ≥3 AEs, %	67.3	70.4	-
Serious AEs, %	42.0	50.0	-
Atrial fibrillation/flutter, %	5.2	13.3	-
Dose interruption, %	50.0	56.8	-
Dose reduction, %	12.3	17.0	-
Death, %	14.7	18.5	-

AE, adverse event; PFS, progression-free survival. [a] By independent review committee; [b] Zanubrutinib, n=327; ibrutinib, n=325; [c] Two-sided *P* value; [d]Zanubrutinib, n=75; ibrutinib, n=75; [e] Nominal *P* value.