ZANUBRUTINIB (ZANU) IN RELATION TO IBRUTINIB (IBR) IMPROVES PFS IN PATIENTS WITH REFRACTORY/RECURRENT (R/R) CLL: FINAL ANALYSIS OF THE ALPINE STUDY

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Introduction: ZANU is a new generation Bruton's tyrosine kinase inhibitor, which: 1) Improves BTK occupancy in disease-relevant tissues and 2) Also presents higher selectivity over other kinases compared to IBR (first generation iBTK). In the phase III ALPINE study (NCT3734016), ZANU was superior to IBR in patients with R/R CLL in predefined interim analysis of the primary endpoint "Overall Response Rate" (ORR) assessed by both the

Independent Review Committee (IRC) and by the researcher. Data from the pre-defined final analysis of the key secondary endpoint of PFS are presented here.

Aim: To evaluate PFS in the ALPINE trial that compares ZANU vs. IBRU in the treatment of R/ R CLL.

Method: The trial included R/R CLL patients with measurable disease, ≥1 prior treatment, and no history of BTKi exposure. A stratification by Age, Geographic Region and alterations in TP53 was carried out. Patients were randomized 1:1 to receive ZANU (N=327) or IBR (N=325) until disease progression or unacceptable toxicity.

Once superiority in the primary endpoint of the study (ORR) was demonstrated, PFS, the key secondary endpoint, was assessed through a predefined hierarchical statistical analysis after reaching 205 events: non-inferiority of ZANU vs IBRU in terms of PFS was assessed and later the superiority based on a p value of 2 “heads” of <0.04996. Other endpoints included Overall Survival (OS) and safety.

Results: After a median follow-up of 29.6 months (cut-off date August 8, 2022), the IRC-assessed PFS was higher for ZANU compared to IBR (HR: 0.65; 95% CI: 0.49- 0.86; p=0.0024) in the intention-to-treat population. At 24 months, the CRI-assessed PFS rate was 79.5% with ZANU and 67.3% with IBR. In predefined major subgroups, PFS consistently favored ZANU vs IBR, including patients with del17p/TP53 mutations (HR: 0.52, 95% CI: 0.30-0.88; PFS at 24 months: 77.6% with ZANU and 55.7% with IBR).

Fewer patients discontinued treatment in the ZANU group (26% vs. 41%), and discontinuation rates for cardiac disorders (0.3% vs. 4.3%), Grade 5 cardiac AEs (0.0 % vs 1.9%), grade ≥3 AE (67% vs 70%), severe AE (42% vs 50%), atrial fibrillation/flutter (5% vs 13%), dose interruption (50% vs 57%), dose reduction (12% vs 17%), and death (15% vs 19%) were lower with ZANU than with IBR. No differences in OS have been observed so far (HR: 0.76; 95% CI: 0.51-1.11).

Conclusions: ALPINE is the first study to demonstrate superiority in terms of PFS and ORR of ZANU vs. IBRU in a direct comparison between two BTKi in patients with R/R CLL. The security profile is also favorable for ZANU.