ASPEN: LONG-TERM FOLLOW-UP RESULTS OF A PHASE 3 RANDOMIZED TRIAL OF ZANUBRUTINIB (ZANU) VS IBRUTINIB (IBR) IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA (WM)

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ABSTRACT

ASPEN is a randomized, open-label, phase 3 study comparing zanu, a potent and selective Bruton tyrosine kinase inhibitor (BTKi), with the first-generation BTKi, ibr, in patients with WM. Data with a median follow-up of 43 months is presented. Patients with *MYD88* mutations were assigned to cohort 1 and randomized 1:1 to receive zanu 160 mg twice daily or ibr 420 mg once daily. Randomization was stratified by *CXCR4* mutational status and lines of prior therapy (0 vs 1-3 vs >3). Patients without *MYD88* mutations were assigned to cohort 2 and received zanu 160 mg twice daily. The primary endpoint was the proportion of patients achieving complete response or very good partial response (CR+VGPR). A total of 201 patients (zanu arm, n=102; ibr arm, n=99) were enrolled in cohort 1 and 28 patients were enrolled in cohort 2. A larger proportion of patients in the zanu arm of cohort 1 vs ibr had *CXCR4* mutations by next-generation

sequencing (32% vs 20%, or 33 of 98 vs 20 of 92 with data available) and were aged >75 years (33% vs 22%). Median duration of treatment was 42 months (zanu) and 41 months (ibr), with 67% and 58% remaining on treatment, respectively. The CR+VGPR rate by investigator assessment was 36% with zanu vs 22% with ibr (*P*=0.02) in cohort 1, and 31% in cohort 2. One patient in cohort 2 achieved CR. In patients with wild type or mutant *CXCR4* from cohort 1, CR+VGPR rates with zanu vs ibr were 45% vs 28% (*P*=0.04) and 21% vs 5% (*P*=0.15), respectively. Median progression-free survival and overall survival were not yet reached. Rates of atrial fibrillation, diarrhea, hypertension, localized infection, hemorrhage, muscle spasms, pneumonia, and adverse events leading to discontinuation or death were lower with zanu vs ibr (table). Exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension were lower with zanu vs ibr (0.2 vs 0.8 and 0.5 vs 1.0 persons per 100 person-months, respectively; *P*<0.05). Rate of neutropenia was higher and rate of grade ≥3 infection was lower with zanu vs ibr. Safety outcomes of zanu were similar between cohorts 1 and 2. ASPEN is the largest phase 3 trial with head-to-head BTKi comparison in WM. At a median follow-up of 43 months, zanu was associated with higher CR+VGPR rate and demonstrated clinically meaningful advantages in long-term safety and tolerability vs ibr.

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Table. Safety Summary

AE (all grade), % of treated patients	Cohort 1 zanu (n=101)	Cohort 1 ibr (n=98)	Cohort 2 zanu (n=28)
AE, grade ≥3	74.3	72.4	71.4
AE leading to discontinuation	8.9	19.4	14.3
Atrial fibrillation / flutter[a]	7.9	23.5	7.1
Diarrhea	21.8	34.7	32.1
Hemorrhage[a] / major bleeding[b]	55.4 / 7.9	62.2 / 12.2	39.3 / 7.1
Hypertension[a]	14.9	25.5	10.7
Muscle spasm	10.9	28.6	14.3
Neutropenia[a]	33.7	19.4	21.4
Infection[a] (grade ≥3) / pneumonia	78.2 (20.8) / 5.0	79.6 (27.6) / 18.4	82.1 (32.1) / 14.3

[a]Grouped term.
[b]Includes grade ≥3 hemorrhage and central nervous system bleeding of any grade.
AE, adverse event; ibr, ibrutinib; zanu, zanubrutinib.