EFFICACY AND SAFETY OF ONCE DAILY (QD) VS TWICE DAILY (BID) ZANUBRUTINIB FOR PATIENTS WITH VARIOUS B-CELL MALIGNANCIES: A COMPARATIVE SUMMARY OF CLINICAL DATA AND EXPOSURE-RESPONSE ANALYSES

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Background: Zanubrutinib (320 mg QD or 160 mg BID) is a next-generation irreversible Bruton tyrosine kinase (BTK) inhibitor approved in various countries for the treatment of relapsed/refractory (R/R) mantle cell lymphoma (MCL), Waldenström macroglobulinemia (WM), marginal zone lymphoma (MZL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). While both QD and BID doses were studied in select phase 1 and 2 zanubrutinib trials, only the BID dose has been used in pivotal clinical studies to date. Thus, a summary of clinical data and analyses between the 2 schedules across various B-cell malignancies is of interest.

Aims: We aimed to conduct a comparative summary of safety and efficacy data between the QD and BID regimens in patients with various B-cell malignancies. In addition, exposure-response (E-R) analyses for safety and efficacy endpoints were conducted to bridge the QD and BID regimen.

Methods: Patients from 5 studies were included in the analysis (monotherapy: BGB-3111-AU-003, BGB-3111-215, BGB-3111-216, BGB-3111-1002; combination with obinutuzumab: BGB-3111-GA-101). The following safety and efficacy endpoints were analyzed: adverse events of special interest (AESI), disease response (overall response rate [ORR], complete response [CR] rate or complete metabolic response, and rate of very good partial response [VGPR] or better for WM). The incidence and severity of AESI were prespecified based on the known toxicity for the BTK inhibitor class, including infections, bleeding, hypertension, atrial fibrillation/flutter, and peripheral blood cytopenias. For the E-R analyses, a population pharmacokinetic (PK) model predicted individual area under the curve (AUC), peak concentration (C_{max}), and minimum observed concentration (C_{min}) values, which were merged with corresponding safety or efficacy data. Then, exposure-efficacy and safety relationships were assessed (eg, probability of response plots and logistic regression model) in patients with MCL, WM, MZL, CLL/SLL and follicular lymphoma (FL) from the 5 zanubrutinib studies described.

Results: A total of 216 patients with various B-cell malignancies receiving zanubrutinib 320 mg QD were identified across 5 studies. There are no marked differences in objective responses observed using QD or BID doses in patients across various indications; while there was a numerical difference, the confidence intervals were overlapping (a subset of efficacy evaluable population, with N≥5 in each indication is summarized [Table]). Similar to the previous report (Ou et al. *Leuk Lymphoma* 2021), comparable safety profiles were observed with both dosing schedules. In 278 patients receiving zanubrutinib BID vs 95 receiving zanubrutinib QD from the BGB-3111-AU-003 study, respectively, rates of ≥1 AE leading to

treatment discontinuation (11.2% vs 8.4), grade ≥3 hemorrhage (4.0% vs 3.2%), grade ≥3 hypertension (4.0% vs 2.1%), and grade ≥3 atrial fibrillation/flutter (1.4% vs 1.1%) were comparable. There were no evident E-R relationships between PK exposure (AUC, C_{max}, or C_{min}) and efficacy endpoints or the probability of having an AESI across indications. Overall, the E-R analysis showed that ORR and adverse event rate was not impacted by C_{max} or C_{min} differences between the QD and BID regimens that have the same total daily dose and AUC.

Summary/Conclusion: Both 320 mg QD and 160 mg BID are safe and effective regimens with high rates of objective response in patients with various B-cell malignancies. Comparison of the ORR between QD and BID dosing did not indicate advantage of either regimen.

Table: Response rates between zanubrutinib 160 mg BID and 320 mg QD doses in patients with B-cell malignancies

Study		160 mg BID	320 mg QD
BGB-3111-AU-003[1-3]	**R/R MCL**	**N=14**	**N=18**
	CR, n (%) (95% CI)	4 (28.6) (8.4, 58.1)	4 (22.2) (6.4, 47.6)
	ORR[a], n (%) (95% CI)	12 (85.7) (57.2, 98.2)	15 (83.3) (58.6, 96.4)
	R/R and TN CLL	**N=81**	**N=40**
	CR, n (%) (95% CI)	11 (13.6) (7.0, 23.0)	9 (22.5) (10.8, 38.5)
	ORR[b], n (%) (95% CI)	76 (93.8) (86.2, 98.0)	40 (100.0) (91.2, 100.0)
	R/R and TN WM	**N=47**	**N=22**
	VGPR + CR rate, n (%) (95% CI)	23 (48.9) (34.1, 63.9)	7 (31.8) (13.9, 54.9)
	ORR[c], n (%) (95% CI)	46 (97.9) (88.7, 99.9)	20 (90.9) (70.8, 98.9)
BGB-3111-GA101-001	**R/R FL**	**N=20**	**N=16**
	CR, n (%) (95% CI)	9 (45) (23.1, 68.5)	7 (43.8) (19.8, 70.1)
	ORR, n (%) (95% CI)	15 (75) (50.9, 91.3)	11 (68.8) (41.3, 89.0)
BGB-3111-215[4]	**WM, CLL/SLL**	**N=40**	**N=24**
	ORR, n (%) (95% CI)	28 (70.0) (53.5, 83.4)	13 (54.2) (32.8, 74.5)
BGB-3111-216[5]	**R/R or TN WM**	**N=41**	**N=9**
	ORR, n (%) (95% CI)	29 (70.7) (54.5, 83.9)	6 (66.7) (29.9, 92.5)
	VGPR, n (%) (95% CI)	13 (31.7) (18.1, 48.1)	3 (33.3) (7.5, 70.1)
BGB-3111-1002[6]	**NHL[d]**	**5**	**5**
	ORR, n (%) (95% CI)	3 (60.0) (14.7, 94.7)	3 (60.0) (14.7, 94.7)

1. Tam et al. *Hematol Oncol* 2019 2. Woyach et al. *Blood* 2019 3. Trotman et al. *Blood* 2020 4. Shadman, et al. *Lancet Oncol* 2023 5. Castillo et al. *EHA* 2022 6. Song et al. *Br J Haematol* 2022
[a]ORR in R/R MCL: the proportion of patients that have an assessment of partial response (PR) and CR.
[b]ORR in R/R and TN CLL/SLL: the proportion of patients that have an assessment of PR with lymphocytosis or higher (PR, VGPR, and CR).
[c]ORR in patients with R/R and treatment-naïve WM: the proportion of patients that have an assessment of minimal response or higher (PR, VGPR, and CR).
[d]Non-Hodgkin lymphoma (NHL) includes FL, MZL, and MCL.