RESULTS OF A PHASE 2 EXPANDED ACCESS STUDY OF ZANUBRUTINIB IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA

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Background: Bruton tyrosine kinase (BTK) inhibition is an emerging standard of care for Waldenström macroglobulinemia (WM). Zanubrutinib (BGB-3111) is a second-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases. Zanubrutinib was recently approved by the United States Food and Drug Administration, Health Canada, and the European Union at a dose of 320 mg once daily (QD) or 160 mg twice daily (BID) for the treatment of adult patients with WM. BGB-3111-216 (NCT04052854) is a single-arm, expanded access study of zanubrutinib for treatment-naïve patients who are unsuitable for standard chemoimmunotherapy or patients with relapsed/refractory WM.

Aims: To provide real-world experience with zanubrutinib in patients with WM.

Methods: Eligible patients with treatment-naïve or relapsed/refractory WM were assigned to receive zanubrutinib at a dose of 320 mg QD or 160 mg BID. The primary endpoint was the number of patients enrolled/treated and the number of enrolling sites. Secondary endpoints of safety and efficacy included selected treatment-emergent adverse events (TEAEs), disease response (overall response rate and very good partial response or better), progression-free survival, and overall survival. Response was evaluated by investigator assessment according to the 6th International Workshop on WM (*Br J Haematol.* 2013;160(2):171-6) every 6 months at minimum. The study was closed by the sponsor in July 2021, and active patients were transitioned to commercial zanubrutinib via a patient-assistance program.

Results: Fifty patients with WM (17 treatment naïve; 33 relapsed/refractory), were enrolled from December 2019 to June 2021 across 10 academic and community medical centers in the United States. At study entry, median age was 72 years, 54% had intermediate-risk disease, 40% had high-risk disease, and median number of prior therapies for patients with

relapsed/refractory disease was 2. Median treatment exposure was 9.2 months (range, 1.4-20.0). Thirty-eight (76%) patients had ≥1 TEAE, and 36 (72%) experienced ≥1 TEAE of special interest (**Table**). Grade ≥3 TEAEs of special interest included hypertension (8%), infection (8%), atrial fibrillation or flutter (2%), neutropenia (2%), and second primary malignancy (2%). No new safety signals were observed. In the 41 patients with ≥1 response evaluation, overall response rate was 85.4% (35; 95% CI: 70.8, 94.4), and major response rate was 73.2% (30; 95% CI: 57.1, 85.8). Overall, 39.0% achieved a best overall response of very good partial response (16; 95% CI: 24.2, 55.5). Of the 4 patients who achieved a best overall response of progressive disease, 3 had IgM values that met partial response criteria before the first 6 months response assessment. Progression-free survival and overall survival were immature due to short follow-up, and the median was not met.

Conclusion: The results of this real-world, expanded-access study were consistent with those of the established zanubrutinib profile in WM and other B-cell malignancies when administered as monotherapy at a daily dose of 320 mg orally (either as 160 mg BID or 320 mg QD) in patients with intermediate or high-risk relapsed/refractory or treatment-naïve WM.

Table. BGB-3111-216 Analyses

Adverse events of interest, n (%) **(Safety population)**	**160 mg BID (n=41)**	**320 mg QD (n=9)**	**Overall (n=50)**
≥1 TEAE of special interest	31 (75.6)	5 (55.6)	36 (72.0)
Grade ≥3	7 (17.1)	1 (11.1)	8 (16.0)
Hypertension	4 (9.8)	0 (0.0)	4 (8.0)
Infection	3 (7.3)	1 (11.1)	4 (8.0)
Atrial fibrillation or flutter	1 (2.4)	0 (0.0)	1 (2.0)
Neutropenia	1 (2.4)	0 (0.0)	1 (2.0)
Second primary malignancy	1 (2.4)	0 (0.0)	1 (2.0)
Best overall response by investigator assessment, n (%) **(Efficacy evaluable population)**	**160 mg BID (n=33)**	**320 mg QD (n=8)**	**Overall (n=41)**
Very good partial response	13 (39.4)	3 (37.5)	16 (39.0)
Partial response	12 (36.4)	2 (25.0)	14 (34.1)
Minor response	4 (12.1)	1 (12.5)	5 (12.2)
Stable disease	1 (3.0)	1 (12.5)	2 (4.9)
Progressive disease	3 (9.1)	1 (12.5)	4 (9.8)
Very good partial response or complete response	13 (39.4)	3 (37.5)	16 (39.0)
Major response rate	25 (75.8)	5 (62.5)	30 (73.2)
Overall response rate	29 (87.9)	6 (75.0)	35 (85.4)

BID, twice daily; QD, once daily; TEAE, treatment-emergent adverse event.