BGB-11417-203, an ongoing, phase 2 study of sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, in patients with Waldenström macroglobulinemia

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Background: Bruton tyrosine kinase (BTK) inhibitors and anti-CD20 antibody–based systemic therapies are included within the preferred treatment algorithms for Waldenström macroglobulinemia (WM). However, to date, no treatments have been approved for patients with WM that is refractory to both BTK inhibitors and anti-CD20–based therapy. Venetoclax, the first-generation BCL2 inhibitor, has demonstrated clinical activity in patients with relapsed/refractory (R/R) WM (Castillo et al. *J Clin Oncol*. 2022), but venetoclax has no regulatory approvals in WM. Sonrotoclax, a next-generation BCL2 inhibitor, is more selective and a more pharmacologically potent inhibitor of BCL2 than venetoclax. In a phase 1 trial, sonrotoclax monotherapy was well tolerated at all tested dose levels ≤640 mg and showed promising evidence of antitumor activity in patients with R/R WM (Soumerai et al. *Blood*. 2022). Based on the data from these earlier studies, a phase 2 study of sonrotoclax monotherapy in patients with R/R WM has been initiated and is currently recruiting.

Methods: BGB-11417-203 (NCT05952037) is an open-label, international, phase 2 study. Eligible patients have histologically confirmed WM that is R/R to both BTK inhibitor therapy and anti-CD20–based systemic therapy combined with chemotherapy or a proteasome inhibitor (PI; cohort 1); R/R to anti-CD20–based systemic therapy combined with chemotherapy or a PI and intolerance of BTK inhibitor therapy (cohort 2); or R/R to a BTK

inhibitor and unsuitable for chemoimmunotherapy (cohort 3). Patients who have received previous treatment with a BCL2 inhibitor are ineligible. Approximately 85 patients will be enrolled across cohorts to receive sonrotoclax until disease progression, death, unacceptable toxicity, patient withdrawal, loss to follow-up, or study termination. The primary endpoint is major response rate (MRR; defined as partial response or better) in cohort 1 per IWWM-11 criteria, as assessed by an independent review committee (IRC). Key secondary endpoints include MRR assessed by investigator (INV) in cohort 1 and by IRC and INV in both cohorts 2 and 3; overall response rate, duration of response, and progression-free survival by IRC and INV; overall survival; and safety and tolerability. Patient recruitment is ongoing in Australia, the US, China, and Europe.