Real-World Effectiveness and Safety of Zanubrutinib in Waldenström Macroglobulinemia: Results From the Belgian WIZARD Study

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Background: Zanubrutinib is a potent, highly selective, irreversible, second-generation Bruton tyrosine kinase (BTK) inhibitor. In the pivotal phase 3 ASPEN trial, zanubrutinib demonstrated high efficacy and favorable tolerability in patients with Waldenström macroglobulinemia (WM), establishing it as a standard BTK inhibitor in this setting. In November 2021, the European Medicines Agency approved zanubrutinib for adult patients with WM who had received at least one prior therapy or as first-line treatment in patients unsuitable for immunochemotherapy.

Aims: The multicenter, observational WIZARD study collected Belgian real-world data on the efficacy and safety of zanubrutinib in adult WM patients.

Methods: WIZARD was a retrospective and prospective, multicenter, observational study conducted in Belgium. Eligible participants were adult patients with symptomatic WM who had received zanubrutinib in accordance with Belgian reimbursement criteria, with treatment initiated between October 1, 2022 and September 1, 2024. The primary objective was to evaluate the real-world effectiveness of zanubrutinib, assessed by major response rate (MRR), overall response rate (ORR), best individual response, and progression-free survival (PFS). Secondary objectives included time to (patient best) response, (best) response duration, overall survival (OS), and time to next treatment. This abstract describes the efficacy and safety results in the overall study population and across selected subgroups.

Results: Eighty-nine patients were included, with a median age of 76 years and a median of two prior treatment lines; 37 patients (41.6%) received zanubrutinib in first line, and 20 (22.5%) had previously received an ibrutinib-containing regimen. An *MYD88* mutation was confirmed in 56 patients (62.9%) (5 patients [5.6%] were *MYD88* wildtype; *MYD88* mutation status was not available/unknown in 28 patients [31.5%]). The MRR and ORR for the overall study population were 64.0% (95% CI, 53.2%-73.9%) and 77.5% (95% CI, 67.4%-85.7%), respectively, with 23 patients (25.8%) achieving at least a very good partial response. In patients with prior ibrutinib treatment, the MRR was 45.0% and ORR was 60.0%. At 1 and 2 years, PFS rates were 83.1% and 67.1%, respectively, with corresponding OS rates of 89.8% and 81.4%. Efficacy outcomes were consistent across investigated subgroups (**Table**), with high response rates and comparable PFS and OS results in older patients (≥75 years) relative to their younger

counterparts. Zanubrutinib also demonstrated similar effectiveness in treatment-naive and previously treated populations, with high response rates irrespective of *MYD88* mutation status. The treatment was well tolerated, with hematoma (n=5) and muscle cramps (n=4) as the most common adverse events (AEs). Grade ≥3 AEs were observed in 8.9% of patients, with 5.6% of patients discontinuing treatment due to AEs.

Conclusions: WIZARD corroborates the efficacy and safety of zanubrutinib in patients with WM in a real-world Belgian setting, irrespective of age, treatment setting, and *MYD88* mutation status. As such, these findings are well in line with outcomes observed in the pivotal ASPEN trial.

Table. Efficacy Across Selected Subgroups in the WIZARD Study

	n	MRR, %	ORR, %	1-y PFS, %	2-y PFS, %	1-y OS, %	2-y OS, %
Overall	89	64.0	77.5	83.1	67.1	89.9	81.4
Age							
≤65 y	13	61.5	76.9	100	74.1	100	100
66-75 y	30	60.0	76.7	80	64.4	96.7	81.8
≥75 y	46	67.4	78.3	80.3	66.7	82.5	77.9
Tx status							
Tx naive	37	67.6	81.1	78.4	53.7	86.5	75.2
Previously treated	52	61.5	75.0	86.4	74.5	92.2	85.9
MYD88 status							
MYD88 mutation	56	64.3	80.4	82.1	63.9	89.3	80.4
MYD88 wt/unknown	33	63.6	72.7	-	-	-	-

Tx, treatment; wt, wild type; yr, year.