Characterization of the safety/tolerability profile of zanubrutinib and comparison with the profile of ibrutinib in patients with B-cell malignancies: post hoc analysis of a large clinical trial safety database

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Introduction: Bruton tyrosine kinase (BTK) is an important regulator of cell proliferation and cell survival in various B-cell malignancies. BTK inhibitors block B-cell receptor–induced BTK activation and its downstream signaling, leading to growth inhibition and cell death in malignant B cells. The first-generation BTK inhibitor, ibrutinib, revolutionized treatment; however, inhibition of off-target kinases such as EGFR, HER2, TEC, and CSK may be associated with toxicities, including gastrointestinal side effects, rash, and atrial fibrillation, that limit its use. Zanubrutinib, a potent and selective next-generation BTK inhibitor, was designed to maximize BTK occupancy and minimize off-target effects. Here, we characterize the overall safety and tolerability of zanubrutinib in patients with B-cell malignancies and compare its profile with ibrutinib.

Methods: In the post hoc analyses, safety data were pooled from 10 zanubrutinib monotherapy clinical trials in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, marginal zone lymphoma, Waldenström macroglobulinemia, follicular lymphoma, and other B-cell malignancies (N=1550), including 2 (ASPEN, ALPINE) that compared zanubrutinib head-to-head with ibrutinib. Incidence rates and exposure-adjusted incidence rates (EAIRs) of treatment-emergent adverse events (TEAEs; summarized in MedDRA preferred terms) and adverse events of special interest (AESIs; defined in grouped terms) were assessed.

Results: Median zanubrutinib exposure was 34.4 months. The most common nonhematologic any-grade TEAEs with zanubrutinib were upper respiratory tract infection (29.7%), diarrhea (21.1%), contusion (19.5%), cough (18.1%), and rash (16.6%). Grade ≥3 TEAEs in ≥5% of patients included pneumonia (8.4%) and hypertension (8.1%). The only serious TEAE in ≥5% of patients was pneumonia (8.2%). In ASPEN/ALPINE, patients treated with zanubrutinib had lower rates of discontinuation (14.1% vs 22.0%), dose reduction (13.9% vs 19.2%), and death (8.7% vs 10.2%) due to TEAEs than those treated with ibrutinib. EAIRs of AESIs were numerically lower with zanubrutinib vs ibrutinib, except for neutropenia (**Table**). With longer follow-up, the prevalence of AESIs with zanubrutinib generally remained constant or decreased.

Conclusions: These pooled safety analyses in patients with B-cell malignancies showed that zanubrutinib is well tolerated, with generally mild to moderate TEAEs and low discontinuation rates due to TEAEs. The prevalence of AESIs generally decreased over time, with no new safety signals emerging. Due to the continuous dosing of BTK inhibitors in most B-cell malignancies, long-term tolerability and low treatment discontinuation rates with BTK inhibitors are important. These analyses support zanubrutinib as an appropriate long-term treatment option for patients with B-cell malignancies.

Table. Exposure-Adjusted Incidence Rates for Adverse Events of Special Interest

	Zanubrutinib (N=1550)	ASPEN/ALPINE[a]	
		Zanubrutinib (n=425)	Ibrutinib (N=422)
Median exposure, mo	34.4	32.6	25.7
Exposure-adjusted incidence rate, persons/100 person-months			
Infections	6.01	5.40	6.64
Opportunistic infections	0.07	0.07	0.13
Hemorrhage	3.00	2.49	3.00
Major hemorrhage	0.17	0.17	0.24
Neutropenia	1.21	1.32	1.05
Thrombocytopenia	0.59	0.49	0.65
Hypertension	0.57	0.82	1.08
Anemia	0.51	0.57	0.75
Second primary malignancies	0.52	0.47	0.58
Skin cancers	0.30	0.27	0.38
Atrial fibrillation/flutter	0.15	0.20	0.64

[a] Head-to-head trials of zanubrutinib vs ibrutinib.