Rate of Cardiac Disorders in Patients With B-Cell Malignancies Who Undergo Treatment With Zanubrutinib

Authors: Han Ma (Senior Vice President, Chief Safety Officer),[1] Constantine S Tam (Director of Haematology),[2] Meng Zhang (Executive Medical Director),[1] Lipeng Chen (Associate Medical Director),[1] Soraya Azmi (Senior Director, Epidemiology),[1] Jun Zhang (Director of Biostatistics),[1] Aileen Cohen (Vice President Clinical Development),[1] Nicola Wallis (Executive Director, Pharmacovigilance Innovation),[1] and Philip T Sager (Adjunct Professor)[3]

Affiliations: [1]BeiGene, Ltd. and BeiGene USA, Inc., San Mateo, CA, USA; [2]The Alfred Hospital, Melbourne, Victoria, Australia; Monash University, Melbourne, Victoria, Australia; and [3]Stanford University School of Medicine, Stanford, CA, USA

Abstract Content: Bruton tyrosine kinase inhibitors (BTKi) have improved treatment of B-cell malignancies, but the first-generation BTKi, ibrutinib, is associated with an increased risk for cardiovascular toxicities such as atrial fibrillation (Afib) and ventricular arrhythmias (VA) (O'Brien et al. *Clin Lymphoma Myeloma Leuk* 2018). Zanubrutinib, an irreversible, potent, next-generation BTKi designed to maximize BTK occupancy and minimize off-target inhibition (Guo et al. *J Med Chem* 2019), has been generally well tolerated in clinical trials. Here we report the occurrence of Afib/flutter and idiopathic VA (IVA; defined as VA in structurally normal hearts without myocardial scarring/active infections) in ALPINE (NCT03734016), ASPEN (NCT03053440), and a pooled analysis of 10 clinical studies of zanubrutinib.

The ALPINE study and ASPEN Cohort 1 compared zanubrutinib with ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or Waldenström macroglobulinemia, respectively. Patients were evaluated for exposure-adjusted incidence rate (EAIR) of Afib and symptomatic (grade ≥2) IVA. Differences in EAIR between zanubrutinib and ibrutinib, based on asymptotic normal distribution, were calculated.

In the pooled analyses, 1550 patients received zanubrutinib as monotherapy, 938 had CLL/SLL (525 relapsed/refractory CLL/SLL), and the median age was 67 years (61% ≥65 years). Most patients were men (66%) and White (67%), with ECOG PS of 0 or 1 (93.9%). Among patients in ALPINE, 5.9% (19/324; zanubrutinib) vs 5.6% (18/324; ibrutinib) had a history of Afib/flutter, whereas 1.9% vs 8.0% experienced a new Afib/flutter event (median exposure 13.5 and 12.8 months, respectively). Among patients in ASPEN (Cohort 1), 9.9% (10/101; zanubrutinib) vs 8.2% (8/98; ibrutinib) had a history of Afib/flutter and 5.9% vs 22.4% experienced a new Afib/flutter event (median exposure 35.0 and 34.6 months), respectively. The EAIR of Afib/flutter per 100 person-month was significantly lower with zanubrutinib than ibrutinib in the pooled analyses (0.82 vs 0.13; $P<0.0001$), ALPINE (0.79 vs 0.16; $P=0.0003$) and ASPEN (0.86 vs 0.19; $P=0.0010$). Among patients in ALPINE, 0.6% (2/324; zanubrutinib) vs 0.3% (1/324; ibrutinib) had a history of VA, whereas 0.6% vs 1.5% experienced a new symptomatic IVA event, respectively. In ASPEN, no symptomatic IVA events were reported with zanubrutinib vs 1 (1/98 patients) event with ibrutinib. The EAIR of symptomatic IVA was significantly lower with zanubrutinib vs ibrutinib in the pooled analysis (0.14 vs 0.87; $P=0.0028$) and numerically lower in ALPINE (0.43 vs 1.19; $P=0.2270$).

These findings support the use of zanubrutinib as a treatment option for patients with B-cell malignancies.