Abstract: PB2905

Title: APEX PART 2 TRIAL IN PROGRESS: A RANDOMIZED, PHASE 2 OPEN-LABEL CLINICAL STUDY OF BEZUCLASTINIB IN ADULT PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS

Abstract Type: Publication Only

Topic: Myeloproliferative neoplasms - Clinical

Background:

Systemic mastocytosis (SM) is a rare heterogeneous disease characterized by the aberrant accumulation of neoplastic mast cells (MC). In about 95% of adult patients, SM is driven by a gain-of-function mutation (D816V) in exon 17 of KIT. Advanced SM (AdvSM) is a life-threatening form of SM and includes three subtypes: aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). Despite improvement in disease control with approval of tyrosine kinase inhibitors (TKIs), there is still unmet need for improved tolerability and efficacy in AdvSM treatments. Bezuclastinib is an oral, potent, and selective TKI which potently inhibits KIT D816V. Results from Part 1 of the Apex study in patients with AdvSM treated with the original bezuclastinib formulation were presented previously (Vachhani et al. [abstract] In: Blood (ASH) 2023). Part 1 of the Apex study randomized 32 patients 1:1:1:1 to receive the original bezuclastinib formulation at 50, 100, or 200 mg BID or 400 mg QD, and completed enrollment. Safety in Part 1 was encouraging, with the majority of events being low grade (Gr1/Gr2) and reversible and no related cognitive impairment or bleeding events reported. Clinical activity was promising, with significant reductions in biomarkers of MC activity and a 56% overall response rate (ORR = complete response [CR] + complete remission with partial hematologic recovery [CRh] + partial response [PR] + clinical improvement [CI]) per mIWG-MRT-ECNM criteria and 75% ORR (CR + PR) per pure pathologic response (PPR) criteria. Data from Part 1 suggest that bezuclastinib exposure achieved with 100 mg BID (200 mg/day) of an original formulation resulted in optimal efficacy and safety outcomes. 150 mg QD of the optimized formulation of bezuclastinib is predicted to result in optimal exposure comparable to that achieved with 100 mg BID in Part 1.

Aims:

The Apex study Part 2 (NCT04996875) is designed to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics of bezuclastinib in patients with AdvSM.

Methods:

Apex is a multicenter, randomized Phase 2 open-label study of bezuclastinib in patients with AdvSM per 2022 WHO criteria regardless of prior therapy, including cladribine, TKIs, and interferon.

Based upon efficacy, safety, and PK data from Part 1, Part 2 is actively enrolling approximately 65 patients to be treated with the optimized formulation of bezuclastinib at a dose of 150 mg QD. Additional cohorts include 15 patients without measurable C-findings and 20 patients with high-risk AHN that will be treated with the combination of bezuclastinib 150 mg QD and azacytidine.

Results:

The primary efficacy endpoint of Part 2 is overall response rate (CR, CRh, PR, and CI) according to mIWG-MRT-ECNM response criteria confirmed by a Central Response Review Committee. Safety data will include AEs/SAEs and dose modification frequencies. Biomarkers, including changes in bone marrow MC burden, serum tryptase level, and KIT D816V mutational burden will be assessed. Other measures of efficacy will include PPR and OS. Apex Part 2 is expected to complete enrollment by the end of 2024.

Summary/Conclusion:

The use of agents targeted to the KIT D816V mutation have been associated with improved disease control in

patients with AdvSM but have risks of concerning adverse events. As such, there remains a significant unmet need for novel and effective treatment options targeted to KIT D816V with improved safety profiles. Supported by Part 1 data, Apex Part 2 will further evaluate the efficacy and safety of bezuclastinib at a dose of 150mg QD in patients with AdvSM.

Keywords: Systemic mastocytosis, Mastocytosis, Clinical trial