Abstract: PB2875

Title: AN OPEN-LABEL PHASE 3 STUDY OF BOMEDEMSTAT, A LYSINE-SPECIFIC DEMETHYLASE 1 (LSD1) INHIBITOR, FOR ESSENTIAL THROMBOCYTHEMIA

Abstract Type: Publication Only

Topic: Myeloproliferative neoplasms - Clinical

Background:

Essential thrombocythemia (ET) is a myeloproliferative neoplasm driven by mutations in *JAK2*, *CALR*, and *MPL* that is primarily characterized by clonal thrombocytosis. The treatments that are currently available can prevent thrombotic complications but do not substantially impact the disease course. There remains an unmet need for novel therapies that can alter the natural history of ET. LSD1 is an enzyme that regulates hematopoietic stem cell and progenitor cell proliferation that is overexpressed in various myeloproliferative neoplasms. Bomedemstat is an irreversible inhibitor of LSD1 that has been shown to improve symptoms, durably reduce platelet and white blood cell counts, and reduce mutation burden in a phase 2 study of patients with ET.

Aims:

To present the methodology for a randomized, open-label, phase 3 study (NCT06079879) that has been designed to evaluate the efficacy and safety of bomedemstat versus best available therapy in patients with ET who had an inadequate response to or were intolerant of hydroxyurea.

Methods:

Eligible patients are aged ≥18 years and have a diagnosis of ET per World Health Organization 2016 diagnostic criteria, a bone marrow fibrosis score of 0 or 1, a platelet count of >450 ´ 109/L, and an absolute neutrophil count of ≥0.75 ´ 109/L. All patients must have had an inadequate response or loss of response to their most recent prior therapy for ET and a history of inadequate response to or intolerance of hydroxyurea per modified European LeukemiaNet (ELN) criteria. Patients will be randomly assigned 1:1 to bomedemstat at a starting dose of 50 mg/day orally (titrated to a target platelet count of ≥150 to ≤350 ´ 109/L) or investigator's choice of best available therapy (anagrelide, busulfan, interferon alfa/pegylated interferon alpha, or ruxolitinib). After 52 weeks of treatment, patients receiving best available therapy will be eligible to cross over to bomedemstat at the investigator's discretion and patients in the bomedemstat arm can continue to receive treatment. Maximum time on study treatment is 156 weeks. Randomization will be stratified by hydroxyurea history (inadequate response vs intolerance) and Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 baseline score (≥4 vs <4). Clinic visits will occur every 2 weeks until week 12 and monthly thereafter. Adverse events (AEs) will be monitored for up to 30 days after treatment end. AEs will be graded per NCI CTCAE v5.0 criteria. The primary end point is durable clinicohematologic response rate per modified ELN criteria. Secondary end points are change in fatigue and total symptom from baseline per the MFSAF v4.0, change in total fatigue score from baseline per the PROMIS Fatigue SF-7a scale, duration of clinicohematologic response, duration of hematologic remission, incidence of thrombotic events, incidence of major hemorrhagic events, transformation to post-ET myelofibrosis or myelodysplastic syndrome/acute myeloid leukemia, event-free survival, and safety and tolerability. Exploratory end points include the pharmacokinetics of bomedemstat, the proportion of patients reporting stability or improvement versus decline on the MSAF v4.0 and PROMIS Fatigue SF-7a domains, and identification of molecular biomarkers.

Results:

Approximately 300 patients will be enrolled. Recruitment is currently underway in Australia and Israel.

Summary/Conclusion:

The results of this study will provide clarity on the efficacy and safety of bomedemstat compared with best

available therapy in patients with ET and an inadequate response to or intolerance of hydroxyurea.

Keywords: Myeloproliferative disorder, Essential Thrombocytemia, Thrombocytosis, Phase Ⅲ