P1054 MYLOX-1: AN OPEN-LABEL, PHASE IIA STUDY OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF ORAL LOXL2 INHIBITOR, GB2064, IN MYELOFIBROSIS

Topic: 16. Myeloproliferative neoplasms - Clinical

Claire Harrison1, John Mascarenhas2, Raajit Rampal3, Daniela Cilloni4, Bertil Lindmark5, Bhupinder Singh5, Brian Jacoby5, Srdan Verstovsek6

1 Guy’s and St Thomas Hospital, London, United Kingdom; 2 Icahn School of Medicine at Mount Sinai, New York, United States; 3 Memorial Sloan Kettering, New York, United States; 4 University Hospital San Luigi Gonzaga, Orbassano, Italy; 5 Galecto Inc, Copenhagen, Denmark; 6 MD Anderson Cancer Center, Houston, United States

Background: GB2064 is a high-affinity, selective, pseudo-irreversible, small-molecule inhibitor of LOXL2, a secreted glycoprotein that crosslinks extracellular matrix collagens and elastin which contributes to stiffness and loss of function of fibrotic organs. GB2064 is being developed as an oral treatment for myelofibrosis (MF), a rare myeloproliferative disease with high morbidity and mortality. Janus kinase (JAK) inhibitor therapy has brought significant advancements in the treatment of MF, but a significant proportion of patients would eventually discontinue treatment, predominantly due to the development of cytopenia (Kyukendall et al Ann Hematol 2018). Thus, there remains a substantial unmet need for developing well-tolerated disease-modifying treatments that reduce bone marrow fibrosis to improve haematologic parameters, splenomegaly, symptom burden and quality of life.

Aims: To assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and clinical effects of oral GB2064 (1000 mg twice daily [BID]) dosed for 9 months to participants with primary or secondary myelofibrosis (PMF/SMF).

Methods: Open-label study in 16 adult participants diagnosed with PMF or SMF in accordance with World Health Organization diagnostic criteria (Barbui et al, Blood Cancer 2018; Cruz et al, Expert Rev Hematol 2020), who are not taking a JAK inhibitor and therefore likely to be refractory, intolerant or ineligible for such inhibitors, with Eastern Cooperative Oncology Group performance status 0-2 and clinical laboratory parameters within appropriate limits per protocol. Primary endpoint is safety and tolerability. Safety and tolerability, PK, PD and appropriate MF-specific assessments will take place at all visits, except Day 7, Day 15 and Month 4 when only safety and tolerability will be assessed (Fig A). Bone marrow biopsies, magnetic resonance imaging (MRI) of spleen and quality of life measures, MPN-10 and EQ-5D-5L, are performed at prespecified timepoints within the protocol. Exploratory endpoints include LOXL2 binding assay in the circulation, relationships between PK plasma exposures, PD markers, and markers of clinical activity, fibrosis and inflammation biomarkers (YKL-40, PAI-1, PDGF, CCN2, collagen formation and degradation neoepitopes). The study is not formally powered. Participants who derive benefit may continue therapy for an additional 3 years (Fig B).

Results: More than half of the intended participants have been enrolled and are on treatment with GB2064 as of February 2022. There have been no significant safety concerns observed at a dose of 1000 mg BID to date.

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Summary/Conclusion: MYLOX-1 is designed to explore the safety and clinical effects of GB2064, a novel small-molecule LOXL-2 inhibitor, addressing bone marrow fibrosis as a main element of myelofibrosis, with the aim of decreasing extramedullary haematopoiesis and improving haematological parameters, symptom burden and the quality of life for patients with MF.