MYLOX-1: An Open-Label, Phase IIa Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Oral LOXL2 Inhibitor, GB2064, in Myelofibrosis: Intermediate Assessment

1683

Srdan Verstovsek[1], John Mascarenhas[2], Raajit Rampal[3], Daniela Cilloni[4], Claire N. Harrison[5], Brian Jacoby[6], Robert J. Slack[7], Vassilios Aslanis[6], Bobby Singh[8], Bertil Lindmark[6]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [4]University Hospital San Luigi Gonzaga, Orbassano, Italy; [5]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [6]Galecto Inc., Copenhagen, Denmark; [7]Galecto, Inc., London, United Kingdom; [8]Galecto Inc., Kuala Lumpur, Malaysia

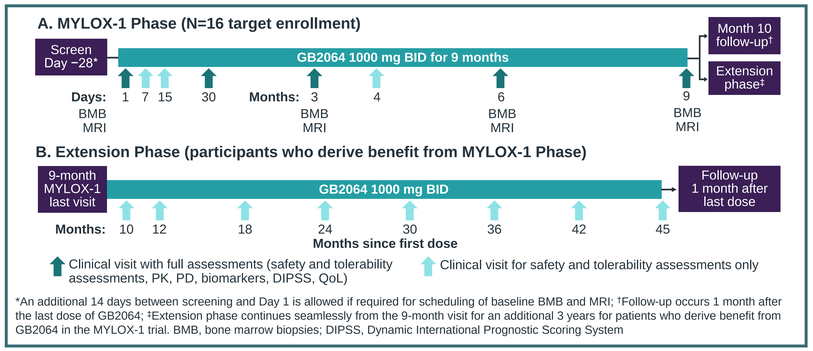
Background

- 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; however, they have relatively modest effects on bone marrow (BM) fibrosis and driver mutation allele burden, and a significant proportion of patients eventually discontinue, predominantly due to the development of cytopenias[1]
- Thus, there is a substantial unmet need to develop well-tolerated disease-modifying treatments that reduce BM fibrosis to improve hematologic parameters, splenomegaly, symptom burden, and quality of life (QoL)
- The MYLOX-1 Phase 2 clinical trial (NCT04679870) aims to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and clinical effects of oral GB2064 (1000 mg two times a day [BID], administered for 9 months), for patients with primary or secondary MF (PMF/SMF). Data presented here are from the intermediate assessment

Methods

- MYLOX-1 is an open-label study, which aims to recruit adults diagnosed with PMF or SMF per World Health Organization diagnostic criteria[2,3] who are not taking a JAK inhibitor, and therefore are likely to be refractory, intolerant, or ineligible for such inhibitors
  - Inclusion criteria: 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 took place at all visits except Day 7, Day 15, and Month 4, when only safety and tolerability were assessed (Figure 1A)
  - BM biopsies, magnetic resonance imaging (MRI) of spleen and QoL measures (myeloproliferative neoplasm-10 and EuroQol-5 dimension-5 levels) were performed at prespecified timepoints
- Exploratory endpoints include LOXL2 binding assay in the circulation, relationships between PK plasma exposure, PD markers, and markers of clinical activity, fibrosis and inflammation biomarkers, PK, PD, and biomarkers in BM biopsies
- Patients who derive benefit may continue therapy for up to 3 additional years (Figure 1B)

Figure 1. MYLOX-1 trial design



An additional 14 days between screening and Day 1 is allowed if required for scheduling of baseline BMB and MRI; †Follow-up occurs 1 month after the last dose of GB2064; ‡Extension phase continues seamlessly from the 9-month visit for an additional 3 years for patients who derive benefit from GB2064 in the MYLOX-1 trial. BMB, bone marrow biopsies; DIPSS, Dynamic International Prognostic Scoring System

Results: intermediate assessment

- Of the 17 patients enrolled at the time of data cut-off for the intermediate assessment (August 11, 2022), 16 initiated GB2064 treatment (median age: 63.5 years; 56% male; 56% with PMF vs. 44% with SMF); 11/16 patients had experienced JAK inhibitor therapy before the trial
- To date, 2 patients have completed treatment, 6 continue to receive treatment and 8 have discontinued therapy (6 due to adverse events [AEs], and 2 due to disease progression)

Summary

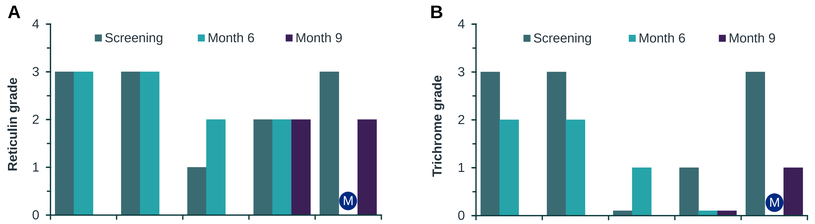
- MYLOX-1 is a Phase 2 clinical trial designed to explore the safety and clinical effects of GB2064, a novel small-molecule LOXL-2 inhibitor, in patients with MF
- At the time of data cut-off for the intermediate assessment (August 11, 2022), a total of 16 patients had initiated GB2064 treatment: 2 have completed treatment, 6 continue to receive treatment and 8 have discontinued treatment
- These data show an improvement in reticulin fibrosis in 1 of the 5 (20%) evaluable patients with MF (who had complete sets of BM biopsies) and a reduction in BM collagen fibrosis in 4 of the 5 (80%) evaluable patients, suggesting that GB2064 could impact the progression of the disease and be disease modifying
- Spleen volume and hematologic parameters (hemoglobin, WBC count, and thrombocytes) stayed stable over the course of the study
- GB2064 penetrated the BM and showed good target engagement in plasma
- GI side effects were reported, but were manageable and low grade in most cases
- GB2064 may prove to be a valid therapeutic option in patients who are ineligible or intolerant to JAK inhibitor therapy

Scan the QR code to access a downloadable version of this poster

BM collagen effects

- BM biopsies at baseline and at 6 months were compared by assessing reticulin and collagen; 5 patients had received therapy for >6 months and had a complete set of BM biopsies at data cut-off
- Of these 5 evaluable patients, 1 (20%) showed improved ≥1 grade reticulin fibrosis and 4 (80%) experienced a ≥1-grade reduction in collagen fibrosis of the BM (Figure 2)

Figure 2. BM biopsies: reticulin staining (A) and collagen trichrome staining (B)



M Missed biopsy due to elective surgery. Note: small bars for patients 3 and 4 in 2b represent scores of 0 (added to make these scores visible)

- The 4 patients who experienced a ≥1-grade reduction in fibrosis score also showed stable spleen volume over the 6-month treatment period (Figure 3) and stable hematologic parameters (hemoglobin, white blood cell [WBC] count, and thrombocytes; Figure 4); none required transfusion
- One patient showed a ≥50% reduction in total symptom score response at Month 6 and another patient showed an anemia response at Month 6. These patients have entered the extension phase of the trial due to the clinical benefit of GB2064 as evaluated by the treating physician (2/4 patients who showed a BM collagen fibrosis response)

Figure 3. Spleen volume

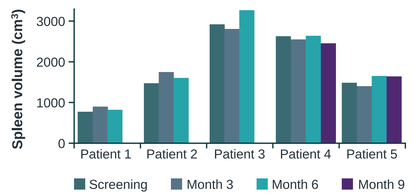
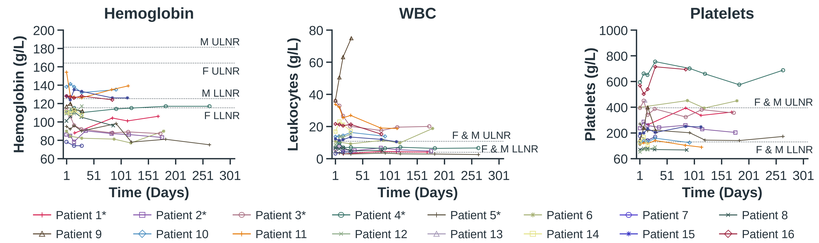


Figure 4. Hematologic parameters

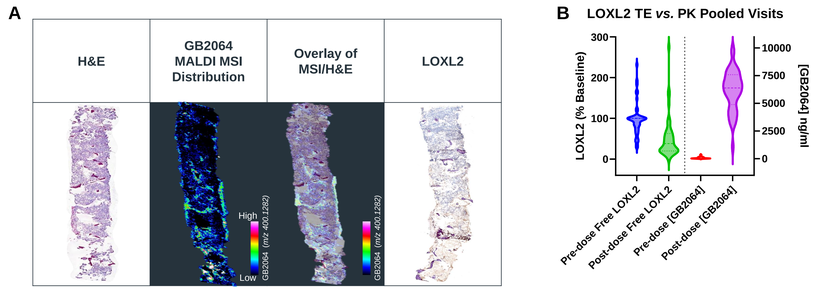


*Patients are the same as those shown in figures 2 and 3. F, female; M, male; LLNR, lower limit of normal range; ULNR, upper limit of normal range

BM penetration of GB2064

- Spatial distribution of GB2064 in Month 3 BM biopsies (2 hours post-dose) showed BM penetration using matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI MSI) (Figure 5A)
- Target engagement was shown in plasma with a 49.5% free LOXL2 decrease from baseline at 2 hours post-dosing (Figure 5B)

Figure 5. Staining for GB2064 penetration in the BM (A) and LOXL2 target engagement in plasma (B)



Note: Brown stain denotes LOXL2 presence. H&E, hematoxylin and eosin staining; TE, target engagement

Safety

- GB2064 has shown an acceptable tolerability profile to date (Table 1)
  - The most common treatment-emergent AEs (TEAEs) were gastrointestinal (GI) in nature (11/16 patients) and were manageable with standard therapy
  - GI-related AEs such as nausea and vomiting (6 patients and 3 patients, respectively, all Grade 1–2) were either self limiting or responded to anti-emetics

Table 1. Safety overview

n (%)	Total number of patients (N=16)	n (%)	Total number of patients (N=16)
Patients with TEAEs	16 (100)	**Patients with TEAEs leading to study drug discontinuation**	8 (50.0)*
Grade 1	12 (75.0)	**Patients with serious TEAEs**	7 (43.8)
Grade 2	14 (87.5)	IMP-related (fall)	1 (6.3)
Grade 3	8 (50.0)	**Patients with fatal unrelated TEAEs**	1 (6.3)
IMP-related	12 (75.0)		

*Safety data cut-off was October 6, 2022. *Includes all patients who experienced a TEAE and discontinued drug; reasons for discontinuation included PD and were not always due to the TEAE. IMP, investigational medicinal product*

Acknowledgements: The MYLOX-1 study is sponsored by Galecto Biotech, AB. Third-party medical writing assistance, under the direction of the authors, was provided by Rachel Dobb, PhD, of Ashfield MedComms, an Inizio company, funded by Galecto Biotech, AB.

References: 1. Kyukendall et al. Ann Hematol. 2018; 2. Barbui et al. Blood Cancer 2018; 3. Cruz et al. Expert Rev Hematol. 2020

This work was sponsored by Galecto Inc.

Presented at the 2022 American Society of Hematology Annual Meeting | December 10–13, 2022