# GB2064 (lenumlostat) shows preliminary evidence of bone marrow collagen fibrosis reduction with manageable tolerability in JAK inhibitor-refractory myelofibrosis: results from the MYLOX-1 phase IIa study

Myelofibrosis is a rare myeloproliferative neoplasm with limited treatment options beyond JAK inhibitors, which provide symptomatic benefit and adequate spleen volume reduction but do not consistently modify underlying disease, including bone marrow fibrosis (BMF).[1] Progressive BMF drives cytopenias and poor prognosis.[2] Lysyl oxidase-like 2 (LOXL2) is a copper-dependent amine oxidase that crosslinks extracellular matrix collagens, contributing to tissue fibrosis.[3] LOXL2 expression is elevated in the bone marrow of patients with primary myelofibrosis but absent in healthy tissue.[4,5] GB2064 is a selective LOXL2 inhibitor with preclinical antifibrotic effects.[6] We report results from MYLOX-1 (NCT04679870), a phase II study evaluating GB2064 in participants with primary or secondary myelofibrosis who were refractory, intolerant, or ineligible for JAK inhibitor therapy.

This open-label, multicenter study enrolled 18 adults with confirmed primary or secondary myelofibrosis (N=9 each), predominantly intermediate-2 risk (67%), and Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (Table 1; *Online Supplementary Figure S1*). The study was conducted in accordance with the Declaration of Helsinki, approved by relevant institutional review boards/ethics committees, and all patients provided written informed consent. Participants included a mix of JAK inhibitor–naïve and previously treated patients, with the majority having refractory or intolerant disease. All harbored at least one driver mutation (*JAK2*$^{V617F}$ 67%, *CALR* 22%, *MPL* 22%), with 38% carrying high molecular risk mutations (*ASXL1*, *EZH2*, *SRSF2*, *IDH*). Participants received GB2064 1,000 mg twice daily orally for 9 months, with an optional extension allowing up to 3 additional years of treatment if participants derive clinical benefit. The selected dose provided greater than 90% inhibitory concentration drug levels at maximum concentration and for 16 hours per 24-hour dosing interval, supported by nonclinical and healthy volunteer data.

The primary endpoints were safety and tolerability. Secondary endpoints included centralized, blinded expert assessment of BMF by bone marrow biopsies at months 6 and 9, hematologic parameters, spleen volume by magnetic resonance imaging, and symptom burden using the MPN10 questionnaire (*Online Supplementary Figure S3*). Recruitment stopped when the predefined target of reduction of collagen fibrosis in at least three of 16 evaluable participants was exceeded.

Seven of the 18 participants completed the study, having remained on treatment for the full 9-month core phase. Twelve participants discontinued from the study due to progressive disease (N=3), withdrawal of consent (N=3), adverse events (N=3), death (N=1), lack of efficacy (N=1), and physician's decision (N=1). One non-treatment-related fatality occurred at month 3 (sepsis with multiorgan failure). The mean duration of treatment was 172.8 days (median 207.0 days, range 4-288).

**Table 1.** Baseline characteristics of the study participants (N=18).

| Characteristic | Value |
|---|---|
| Age, years, median (range) | 64.0 (62.0-73.0) |
| Sex, N (%) | |
| Male | 10 (55.6) |
| Female | 8 (44.4) |
| ECOG PS, N (%) | |
| 0 | 8 (44.4) |
| 1 | 10 (55.6) |
| DIPSS-plus risk category, N (%) | |
| Low | 3 (16.7) |
| Intermediate-1 | 2 (11.1) |
| Intermediate-2 | 12 (66.7) |
| High | 1 (5.6) |
| MF disease type, N (%) | |
| PMF | 9 (50.0) |
| SMF | 9 (50.0) |
| Driver mutations, N (%)[a] | |
| *JAK2*$^{V617F}$ | 12 (67) |
| *CALR* exon 9 | 4 (22) |
| *MPL*$^{515I/K}$ | 4 (22) |
| High molecular risk mutations, N (%) | 7 (38) |
| JAK inhibitor status, N (%)[b] | |
| Naïve | 6 (33) |
| Refractory | 8 (44) |
| Intolerant | 3 (17) |
| RBC transfusion given in the past 12 weeks, N (%) | 4 (22.2) |

[a]Some participants had >1 mutation. These included mutations such as *ASXL1*, *EZH2*, *SRSF2*, and *IDH*. [b]One (6%) participant was ineligible (due to thrombocytopenia). ECOG PS: European Cooperative Oncology Group performance score; DIPSS-plus: Dynamic International Prognostic Scoring System; MF: myelofibrosis; PMF: primary myelofibrosis; SMF: secondary myelofibrosis; RBC: red blood cell.

Among the ten participants evaluable for BMF at month 6, six (60%) demonstrated at least a one-grade reduction in bone marrow collagen fibrosis compared with baseline (Table 3; *Online Supplementary Figure S4*). Notably, this represents a reduction in type 1 collagen, the advanced, therapy-resistant fibrotic component required for the highest fibrosis grade (MF-3) and characteristic of malignant rather than reactive BMF.[7] Two of the ten (20%) showed at least a one-grade reduction in reticulin fibrosis at month 9 (Table 3). All six participants with reduced collagen fibrosis exhibited disease stabilization with stable spleen volume and hematologic parameters over 9 months; none required red blood cell transfusions.

Clinical activity was demonstrated, with responses of modest magnitude. At month 6, clinical responses included one of 18 participants (6%) achieving an anemia response with a 1.8 g/dL hemoglobin increase and one participant (6%) achieving ≥35% spleen volume reduction. Additionally, two participants (11%) attained ≥50% reduction in total symptom score, and two participants (11%) demonstrated improved ECOG performance status. Overall, five participants were deemed by investigators to have derived clinical benefit: of these, four continued into the extension phase, with three maintaining treatment for 20-28 months.

GB2064 demonstrated bone marrow penetration by matrix-assisted laser desorption/ionization mass spectrometry (*Online Supplementary Figure S2*). Plasma pharmacokinetics showed stable concentrations with no additional accumulation beyond steady state. Target engagement was demonstrated with the mean free LOXL2 decreasing from 96.9% pre-dose to 46.6% at 2 hours post-dose. A high inter-individual variability in GB2064 concentration was observed between all analyzed tissues with a coefficient of variation of 89% (N=12). While GB2064 appears to have successfully penetrated the bone marrow, there was no conclusive concentration-response relationship linked to histopathological bone marrow changes.

Treatment-emergent adverse events (TEAE) occurred in 17 of 18 participants (94%) and were predominantly mild to moderate. Gastrointestinal disorders were most common (72%); these were generally self-limiting or responsive to anti-emetic therapy. Four gastrointestinal TEAE in three participants led to discontinuation: grade 3 diarrhea, grade 2 nausea (2 events), and grade 1 vomiting. Nine participants (50%) experienced a grade 3 or higher TEAE. One treatment-related serious adverse event (a fall in an elderly participant) occurred. No significant worsening of anemia or thrombocytopenia was observed. No clinically significant hepatic adverse events occurred except one case of transient grade 2 elevated gamma-glutamyl transferase

**Table 2.** Safety overview for the main study and extension phase.

| AE category | Main study, N=18<br>N (%)[a] |
|---|---|
| Any TEAE | 17 (94.4) |
| Grade 1 | 14 (77.8) |
| Grade 2 | 15 (83.3) |
| ≥Grade 3 | 9 (50.0) |
| Gastrointestinal TEAE | 13 (72.2) |
| GB2064-related TEAE | 12 (66.7) |
| Serious TEAE | 7 (38.9) |
| GB2064-related serious TEAE (fall) | 1 (5.6) |
| TEAE leading to discontinuation | 11 (61.1) |
| Gastrointestinal-related TEAE leading to discontinuation | 3 participants (4 events) |
| Fatal unrelated (sepsis) | 1 (5.6) |
| **AE category** | **Extension part, N=5<br>N of patients (N of events)** |
| TEAE not GB2064-related | 4 (9) |
| Grade 1 | 3 (5) |
| Grade 2 | 2 (4) |
| GB2064-related TEAE | 1 (1) |
| Grade 1[b] | 1 (1) |
| Grade 2 | 0 |
| TEAE possibly GB2064-related[c] | 2 (2) |
| Grade 1 | 1 (1) |
| Grade 2 | 1 (1) |

[a]Participants who experienced more than one treatment-emergent adverse event (TEAE) were counted only once in each row. Where it was not possible to define an adverse event (AE) as treatment-emergent or not, the AE was classified by the worst case. [b]Dysgeusia. [c]Lack of appetite (grade 1) and gastrointestinal discomfort (grade 2) – the latter was the only TEAE that led to a participant being discontinued from the extension part (after approximately 21 months in this part).

**Table 3.** Bone marrow fibrosis response and clinical outcomes.

| Outcome | N/N (%) |
|---|---|
| ≥1 grade reduction in collagen fibrosis (month 6)[a] | 6/10 (60) |
| ≥1 grade reduction in reticulin fibrosis (month 9)[a] | 2/10 (20) |
| Anemia response (month 6) | 1/18 (6) |
| ≥35% spleen volume reduction (month 6)[b] | 1/18 (6) |
| ≥50% symptom score reduction (month 6) | 2/18 (11) |
| Improved ECOG PS score | 2/18 (11) |
| Clinical benefit (investigator-assessed) | 5/18 (28) |
| Continued to the extension phase | 4/5 (80)[c] |

[a]An evaluable participant is defined as a participant who completes at least 6 months of therapy and has at least an evaluable baseline and 6-month bone marrow biopsy. [b]Two of 13 participants achieved >35% reduction by imaging, but only one was assessed as a spleen response by the investigator. [c]One participant did not proceed per the physician's decision despite clinical benefit.

and alkaline phosphatase (month 1, cause unknown, resolved while continuing treatment). During the extension phase, GB2064 was well tolerated with no serious adverse events and no new gastrointestinal events or transfusion requirements (Table 2).

Several design considerations warrant acknowledgment. First, the sample size of the study was small (N=18), while minimizing experimental exposure in this JAK inhibitor-refractory, intolerant and ineligible population. Second, while clinical responses were modest in magnitude and frequency, the finding that six out of ten evaluable patients achieved meaningful collagen fibrosis reduction, accompanied by disease stabilization and acceptable tolerability, provides encouraging preliminary evidence of disease-modifying potential in this treatment-refractory population and supports further investigation in adequately powered, controlled trials. The extension phase study design did not include bone marrow biopsies in order to prioritize collection of comprehensive safety data; consequently, the duration of any improvement in fibrosis was not evaluable. Fibrosis assessment was planned for the subsequent study with anticipated participant rollover.

The reduction specifically in collagen fibrosis is clinically significant and distinguishes GB2064 from existing therapies. While JAK inhibitors provide symptomatic benefits,[8,9] their effects on BMF are limited and inconsistent,[10] particularly pertaining to collagen fibrosis, which represents an advanced, irreversible-appearing fibrotic change in myelofibrosis. The ability of GB2064 to reverse type 1 collagen deposition, not merely reticulin fibrosis, may suggest true disease modification rather than symptomatic palliation alone.

Emerging evidence suggests that BMF score changes may serve as a surrogate endpoint for disease modification, with worsening fibrosis correlating with shorter survival.[11-14] Disease stabilization in fibrosis responders, in whom progression would typically occur in this high-risk population, supports potential disease-modifying effects of LOXL2 inhibition.

In summary, GB2064 demonstrated acceptable safety and tolerability with manageable gastrointestinal adverse events and no significant cytopenias. Bone marrow penetration, target engagement, and reduction of collagen fibrosis in 60% of evaluable participants suggest potential disease-modifying activity. Despite a small sample size and modest clinical response rates, these findings support further investigation of LOXL2 inhibition in myelofibrosis, particularly in combination with JAK inhibitors or other agents.

## Authors

Richard F. Schlenk,[1] Claire N. Harrison,[2] Francesca Palandri,[3] Marco De Gobbi,[4] Federico Itri,[4] Raajit Rampal,[5] Dipti Talaulikar,[6,7] Brian Jacoby,[8] Vassilios Aslanis,[8] Robert J. Slack,[8] James A. Roper,[8] Hans T. Schambye,[8] Bhupinder Singh[9] and John Mascarenhas[10]

[1]Department of Hematology, Oncology, and Rheumatology, Heidelberg University Hospital, Heidelberg, Germany; [2]Guy's and St Thomas' NHS Foundation Trust, London, UK; [3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [4]Azienda Ospedaliero-Universitaria San Luigi Gonzaga, Orbassano, Italy; [5]Memorial Sloan Kettering, New York, NY, USA; [6]Academic Specialist Center, ACT Canberra, Australia; [7]Australian National University, Canberra, Australia; [8]Galecto Inc, Copenhagen, Denmark; [9]Galecto Inc, Kuala Lumpur, Malaysia and [10]Icahn School of Medicine at Mount Sinai, New York, NY, USA

Correspondence:
R.F. SCHLENK - Richard.schlenk@nct-heidelberg.de

https://doi.org/10.3324/haematol.2025.289108

Received: September 8, 2025.
Accepted: February 24, 2026.
Early view: March 5, 2026.



**Disclosures**

HTS, BJ, VA, JAR, RJS, and BS were employed by Galecto Inc during the conduct of this study. JM has received research funding and consulting fees from multiple pharmaceutical companies, including Galecto Inc. FI has received honoraria from multiple pharmaceutical companies. RFS or his institution has received grants and consulting fees from multiple pharmaceutical companies. FP, MDG, CNH, and DT have no conflicts of interest to disclose.

**Contributions**

All authors were involved in the acquisition and analysis of data, and drafting and critical revision of the manuscript, as well as approving the final proof for publishing. HTS, BS and RSl were also involved in the study design.

**Funding**

This study was funded by Galecto Inc (Copenhagen, Denmark). Medical writing and editorial support in the form of developing the draft outline and full manuscript, assembling tables, editing figures and collating authors' comments were provided by Dr Kathryn White of Cathean Ltd. and was funded by Galecto Inc.

**Data-sharing statement**

The protocol for this study is available on request by contacting the corresponding author.

## References


1. Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(5):801-821.
2. Abou Zahr A, Salama ME, Carreau N, et al. Bone marrow fibrosis in myelofibrosis: pathogenesis, prognosis and targeted strategies. Haematologica. 2016;101(6):660-671.
3. Piasecki A, Leiva O, Ravid K. Lysyl oxidase inhibition in primary myelofibrosis: a renewed strategy. Arch Stem Cell Ther. 2020;1(1):23-27.
4. Tadmor T, Bejar J, Attias D, et al. The expression of lysyl-oxidase gene family members in myeloproliferative neoplasms. Am J Hematol. 2013;88(5):355-358.
5. Martinaud C, Desterke C, Konopacki J, et al. Transcriptome analysis of bone marrow mesenchymal stromal cells from patients with primary myelofibrosis. Genom Data. 2015;5:1-2.
6. Rowbottom MW, Bain G, Calderon I, et al. Identification of 4-(aminomethyl)-6-trifluoromethyl)-2-(phenoxy)pyridine derivatives as potent, selective, and orally efficacious inhibitors of the copper-dependent amine oxidase, lysyl oxidase-like 2 (LOXL2). J Med Chem. 2017;60(10):4403-4423.
7. Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A. European Consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 2005;90(8):1128-1132.
8. Harrison C, Kiladijian J-J, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012;366(9):787-798.
9. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366(9):799-807.
10. Harrison CN, Kiladjian J-J, Koschmieder S, Passamonti F. Myelofibrosis: current unmet needs, emerging treatments, and future perspectives. Cancer. 2024;130(12):2091-2097.
11. Guglielmelli P, Rotunno G, Pacilli A, et al. Prognostic impact of bone marrow fibrosis in primary myelofibrosis. A study of AGIMM group on 490 patients. Am J Hematol. 2016;91(9):918-922.
12. Yacoub A, Borate U, Rampal RK, et al. Phase 2 study of add-on parsaclisib for patients with myelofibrosis and suboptimal response to ruxolitinib: final results. Blood Adv. 2024;8(6):1515-1528.
13. Mascarenhas J, Komrokji RS, Palandri F, et al. Randomized, single-blind, multicenter phase II study of two doses of imetelstat in relapsed or refractory myelofibrosis. J Clin Oncol. 2021;39(26):2881-2892.
14. Harrison CN, Garcia JS, Somervaille TCP, et al. Addition of navitoclax to ongoing ruxolitinib therapy for patients with myelofibrosis with progression or suboptimal response: phase II safety and efficacy. J Clin Oncol. 2022;40(15):1671-1680.