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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

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Conflicts of Interest: HS, BJ, VA, JR, RS, and BS were employed by Galecto Inc during study conduct. JM has received research funding and consulting fees from multiple pharmaceutical companies, including Galecto Inc. FI has received honoraria from multiple pharmaceutical companies. RS or his institution has received grants and consulting fees from multiple pharmaceutical companies. FP, MDG, CH, and DT report no conflicts relevant to this study.

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Authors' contributions: All authors were involved in the acquisition and analysis of data, and the drafting and critical revision of the manuscript, as well as approving the final proof for publishing. HS, BS and RS were also involved in the study design.

Data-sharing statement:

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

Dear Editor,

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

This open-label, multicentre study enrolled 18 adults with confirmed primary MF or secondary MF (nine each), predominantly intermediate-2 risk (67%), and Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (Table 1; Supplementary Figure 1). 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 harboured 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 1000 mg twice daily orally for nine months, with an optional extension allowing up to three 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 endpoint was 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 (Supplementary Figure 3). Recruitment stopped when the predefined target of collagen fibrosis reduction 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 nine-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 decision (n=1). One non-treatment-related fatality occurred at Month 3 (sepsis with multiorgan failure). Mean treatment duration was 172.8 days (median 207.0 days, range 4-288).

Among the ten participants evaluable for BMF assessment at Month 6, six (60%) demonstrated at least one-grade reduction in bone marrow collagen fibrosis compared with baseline (Table 3; Supplementary Figure 4). 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 ten (20%) showed at least one-grade reticulin fibrosis reduction at Month 9 (Table3). All six participants with reduced collagen fibrosis exhibited disease stabilization with stable spleen volume and hematologic parameters over nine 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 anaemia response with a 1.8 g/dL haemoglobin increase and one participant (6%) achieving ≥35% SVR. 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 (Supplementary Figure 2). Plasma pharmacokinetics showed stable concentrations with no additional accumulation beyond steady state. Target engagement was demonstrated with mean free LOXL2 decreasing from 96.9% pre-dose to 46.6% two hours post-dose. A high inter-individual variability in GB2064 concentration was observed between all analysed tissues with a coefficient of variation of 89% (n=12). While GB2064 appears to have successfully penetrated the BM, there was no conclusive concentration-response relationship linked to histopathological BM changes.

Treatment-emergent adverse events (TEAEs) occurred in 17 of 18 participants (94%), predominantly mild to moderate. Gastrointestinal disorders were most common (72%), generally self-limiting or responsive to antiemetic therapy. Four gastrointestinal TEAEs in three participants led to discontinuation: Grade 3 diarrhoea, Grade 2 nausea (two events), and Grade 1 vomiting. Nine participants (50%) experienced Grade 3 or higher TEAEs. One treatment-related serious adverse event (a fall in an elderly participant) occurred. No significant worsening of anaemia or thrombocytopenia was observed. No clinically significant hepatic adverse events occurred except one case of transient Grade 2 elevated gamma-glutamyl transferase 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 study employed a small sample size (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 10 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 to prioritize comprehensive safety data collection; consequently, assessment of fibrosis improvement duration 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 JAKi provides 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 changes in MF. GB2064's ability to reverse type 1 collagen deposition, not merely reticulin fibrosis alone, may suggest true disease modification rather than symptomatic palliation alone.

Emerging evidence suggests 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, where 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 cytopenia's. Bone marrow penetration, target

engagement, and collagen fibrosis reduction 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 MF, particularly in combination with JAKi or other agents.

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Tables

Characteristic	Value
Median age (range), years	64.0 (62.0-73.0)
Male, n (%)	10 (55.6)
Female, n (%)	8 (44.4)
ECOG PS 0, n (%) ECOG PS 1, n (%)	8 (44.4) 10 (55.6)
DIPSS-plus risk category, n (%): Low Intermediate-1 Intermediate-2 High	3 (16.7) 2 (11.1) 12 (66.7) 1 (5.6)
MF disease type, n (%): PMF SMF	9 (50.0) 9 (50.0)
Driver mutations, n (%):[a] JAK2V617F CALR exon 9 MPL515l/K	12 (67) 4 (22) 4 (22)
High molecular risk mutations, n (%)	7 (38)
JAKi status, n (%):[b] Naïve Refractory Intolerant	6 (33) 8 (44) 3 (17)
RBC transfusion given in the past 12 weeks, n (%)	4 (22.2)

Table 1. Baseline Characteristics (N=18)

a. Some participants exhibited >1 mutation. This included mutations such as ASXL1, EZH2, SRSF2, and IDH.
b. 1 (6%) participant was ineligible (due to thrombocytopenia).

DIPSS-plus: Dynamic International Prognostic Scoring System; ECOG PS: European Cooperative Oncology Group performance score; JAKi: JAK inhibitor; MF: myelofibrosis; PMF: primary myelofibrosis; PS: performance score; RBC: red blood cells; SMF: secondary myelofibrosis.

Adverse Event Category	Main Study (N=18)[a] n (%)
Any TEAEs	17 (94.4)
Grade 1	14 (77.8)
Grade 2	15 (83.3)
≥Grade 3	9 (50.0)
Gastrointestinal TEAEs	13 (72.2)
GB2064-related TEAE	12 (66.7)
Serious TEAEs	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)

Adverse Event Category	Extension part (N=5) (Number of events)
TEAEs not GB2064-related	4 (9)
Grade 1	3 (5)
Grade 2	2 (4)
GB2064-related TEAEs	1 (1)
Grade 1[b]	1 (1)
Grade 2	0
TEAEs possibly GB2064-related[c]	2 (2)
Grade 1	1 (1)
Grade 2	1 (1)

Table 2. Safety Overview for the Main Study and Extension Phase

a) Participants who experienced more than one 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 which led to a participant being discontinued from the extension part (after approximately 21 months in this part).

TEAE: treatment-emergent adverse event.

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)
Anaemia 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 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 BMB.

b 2/13 participants achieved >35% reduction by imaging, but only one was assessed as spleen response by the investigator.

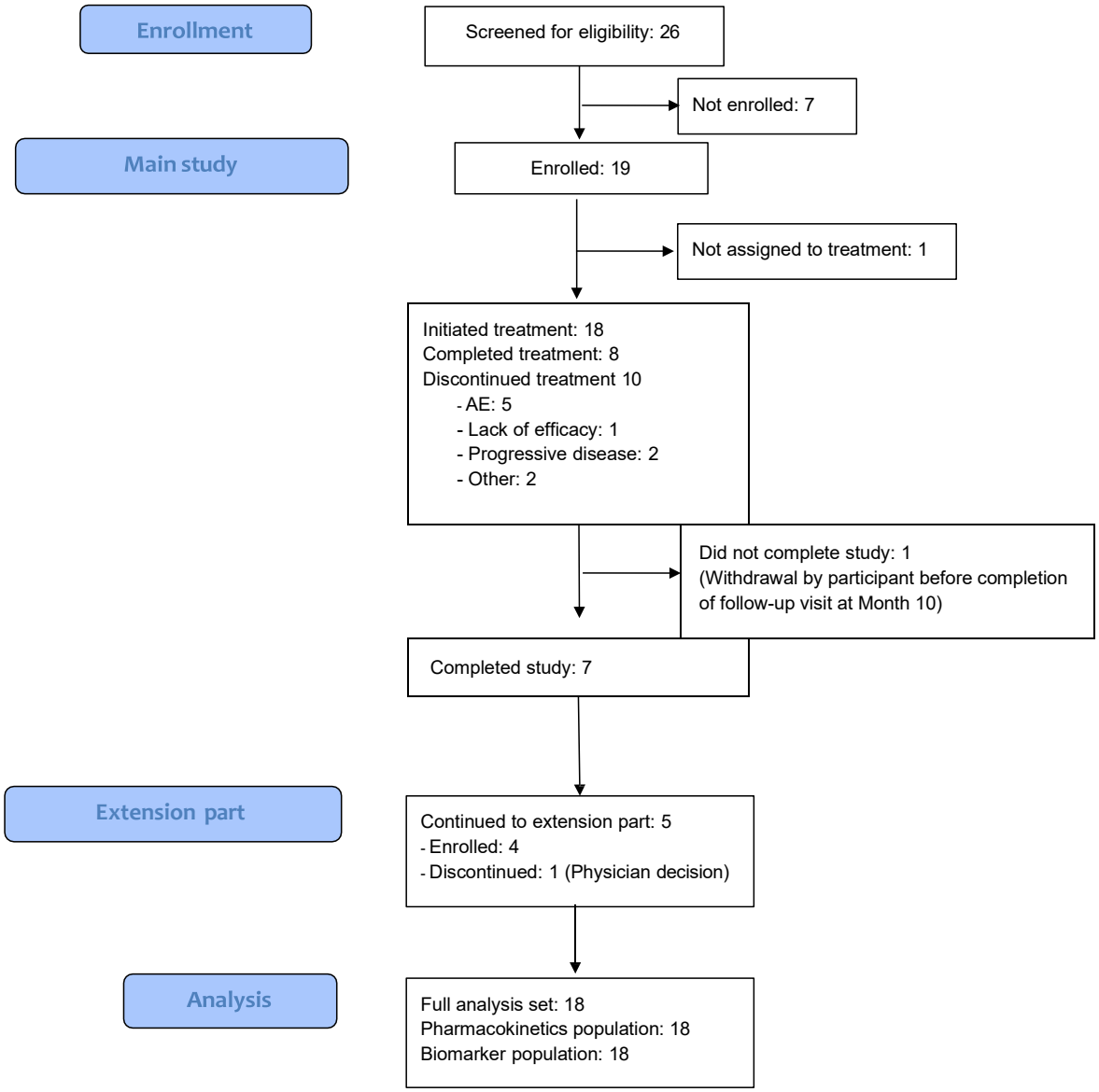
c One participant did not proceed per the physician's decision despite clinical benefit.

Supplementary Figure Legends

Figure 1	Consolidated Standards of Reporting Trials (CONSORT) flow diagram
Figure 2	Representative matrix-assisted laser desorption/ionization mass spectrometry image of A) GB2064 penetration in bone marrow for a single participant at Month 3 and B) lysyl oxidase-2 target engagement in plasma for all participants
Figure 3	Patient-reported outcomes for a) Myeloproliferative Neoplasm (MPN)10 total score - percentage change from baseline (Screening Visit). and b) EQ-5D-5L score percentage change from baseline (Screening Visit). For both graphs, values were computed on available participants with post-baseline visits (full analysis set)
Figure 4	Bone Marrow Collagen Fibrosis Changes from Baseline

Supplementary Figures

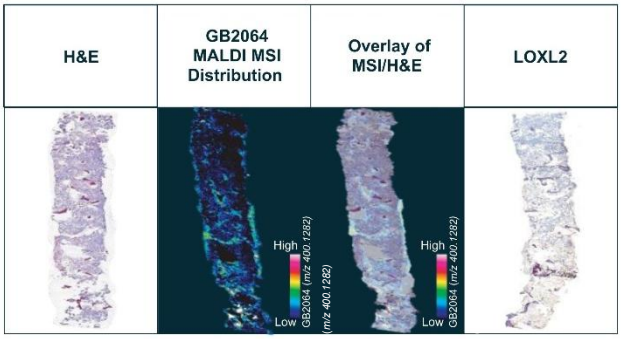
Supplementary Figure 1



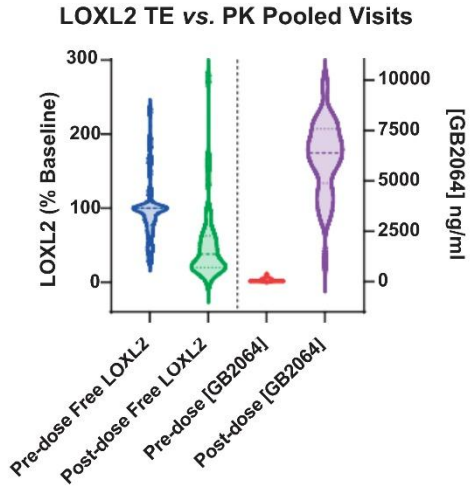
Full analysis set: included all participants who received ≥1 dose of GB2064 and was the primary analysis set used for assessment of safety, tolerability and baseline population characteristics.
Pharmacokinetics population: included all participants who received ≥1 dose of GB2064 and had ≥1 evaluable post-dose pharmacokinetics sample.
Biomarker population: included all participants who received ≥1 dose of GB2064 and had ≥1 evaluable post-dose biomarker assessment.

Supplementary Figure 2

2a



2b

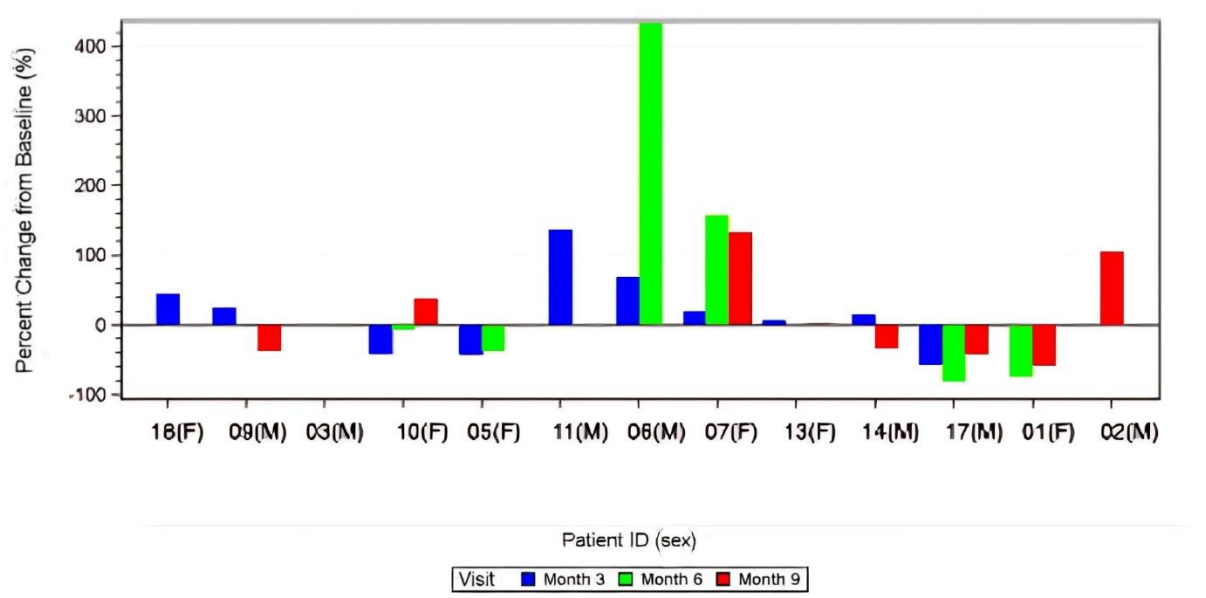


Note: Brown stain denotes LOXL2 presence.

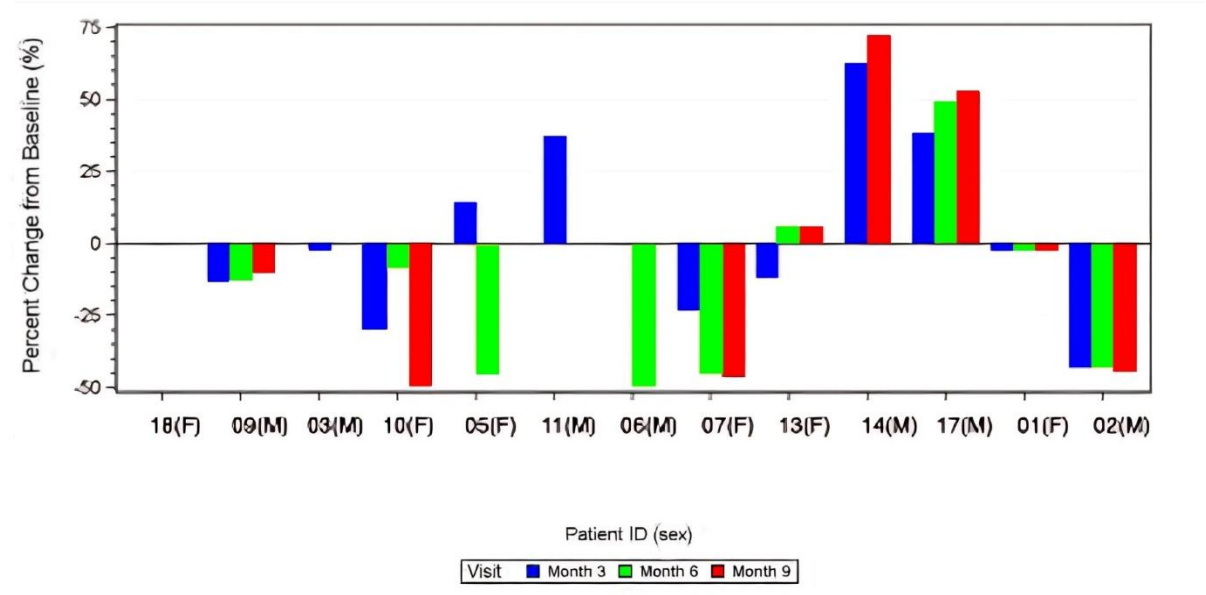
H&E: hematoxylin and eosin staining; LOXL2: lysyl oxidase-2; MALDI: matrix-assisted laser desorption/ionization; MSI: mass spectrometry imaging; PK: pharmacokinetics; TE: target engagement

Supplementary Figure 3

3a



3b



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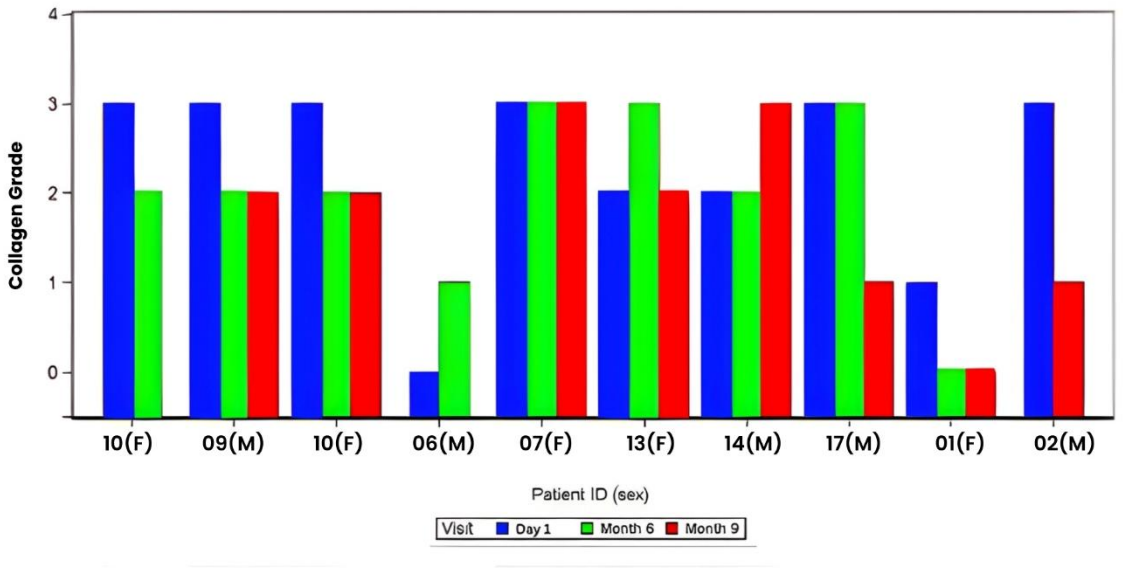
Supplementary Figure 4



F: female; ID: identification; M: male