Breaking the Limits of LSD1 Inhibition: Dual LSD1/HDAC6 Epigenetic Targeting with JBI-802 in MPNs

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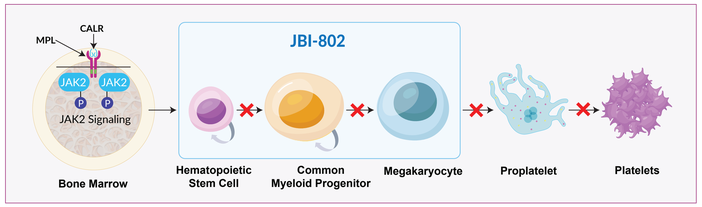
Introduction

JBI-802 is the only oral dual LSD1/HDAC6 (CoREST) inhibitor currently in clinical development and represents a novel epigenetic approach to the treatment of myeloproliferative neoplasms (MPNs)[1]. Both LSD1 and HDAC6 play important and complementary roles in the regulation of hematopoietic differentiation, megakaryopoiesis, inflammatory signaling, and maintenance of the malignant clone[2,3]. Simultaneous inhibition of these targets may provide broader biological activity than selective inhibition of either pathway alone. JBI-802 has a short half-life of 1.5–2 hours, and is rapidly cleared. Emerging clinical data support the continued investigation of JBI-802 as a potential disease-modifying therapy for patients with MPNs.

CoREST Dual LSD1 & HDAC6 Inhibition

- LSD1 functions as critical downstream effectors of the driver mutations - CALR, MPL and JAK2.[2]
- HDAC6 is highly expressed in platelets and regulates the production and function of platelets.[4-6]

Figure 1.



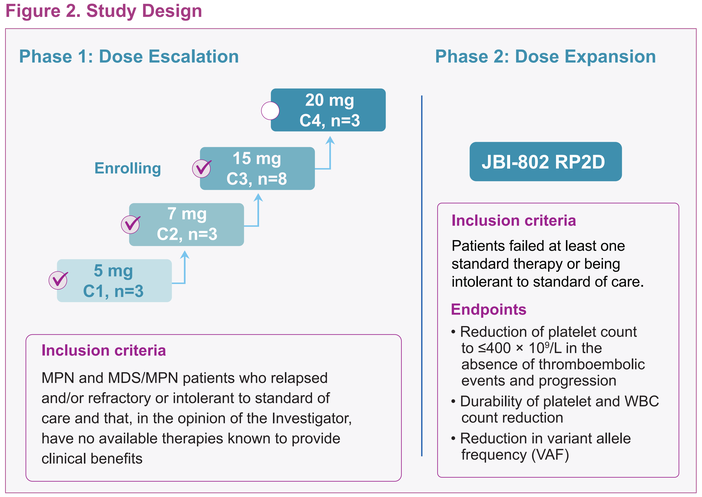
Study Design

Ongoing Phase 1/2, Open Label Multicenter Study of Oral JBI-802

Objectives

- Evaluate safety and tolerability
- Identify MTD and/or establish recommended Phase 2 dose regimen(s)
- Demonstrate preliminary evidence of efficacy at RP2D via reduction of platelet count

Figure 2. Study Design



Efficacy

- 12 patients in dose-escalation received JBI-802 across 4 doses (5, 7, 15, and 20 mg).
- JBI-802 is administered orally once daily in continuous 28-day cycles. Data cut 30 June 2026

Table 1. Dose Escalation Across Four Dose Cohorts (n=12)

Dose	Patient #	Diagnosis	Mutation	# of prior treatments	Baseline Platelets (x10⁹/L)	Max Platelet Reduction (%) within 30 days (x10⁹/L)	Max Platelet Reduction (%) during treatment (x10⁹/L)	Dose modifications
5 mg	1	ET	CALR non-type 1	2	1,295	61	84	to 7 mg @ wk 40 to 5 mg @ wk 92
	2	ET	CALR non-type 1	3	451	0	69	to 7 mg @ wk 40 to 15 mg @ wk 60
	3	ET	JAK2V617F	1	491	16	36	none
7 mg	4	MDS / MPN	JAK2V617F	2	1,199	18	23	none
	5	ET	MPL	1	1,092	30	72	to 15 mg @ wk 49
	6	Post-ET MF	JAK2V617F	3	963	5	40	to 15 mg @ wk 37
15 mg	7	PV	JAK2V617F	3	1,096	75	82	none
	8	ET	CALR Type 1	2	1,720	72	91	none
	9	ET	JAK2V617F	1	674	81	88	to 7 mg @ wk 12 to 5 mg @ wk 20 to 3 mg @ wk 24 to 5 mg @ wk 25
20 mg	10	ET	CALR non-type 1	1	744	39	42	none
	11	ET	JAK2V617F	1	539	85	66	to 10 mg @ wk 3
	12	ET	CALR Type I	1	765	No data	No data	none

Safety

- No DLTs were observed during the 28-day observation period at the 5 mg, 7 mg, and 15 mg dose levels.
- A DLT of thrombocytopenia, consistent with on-target pharmacology, was observed at the 20 mg dose and safely managed with protocol- defined measures.
- Most treatment-emergent adverse events were Grade 1/2
- 2 patients (ET and MDS/MPN) experienced ≥ Grade 3 adverse event
- One patient with MDS/MPN reported two SAEs of ANCA vasculitis and duodenal hemorrhage deemed unlikely related per Investigator.
- No patient discontinued treatment due to thrombocytopenia or treatment-related adverse event

Table 2. Safety Summary

AE Category	5 mg n=3	7 mg n=3	15 mg n=3	20 mg n=3
All TEAES	3 (100%)	3 (100%)	3 (100%)	3* (100%)
All related TEAEs	2 (66.7%)	3 (100%)	1 (33.3%)	2 (66.7%)
Grade 3 and above	1† (33.3%)	1‡ (33.3%)	0	0
SAE	0	1 (33.3%)	0	0
Leading to discontinuation	0	1§ (33.3%)	0	0
Leading to Dose Reduction	0	0	0	0

*One patient withdrew consent after 4 days of treatment-not related to the drug treatment
†Neutropenia
‡Anemia
§Patient withdrew consent after 10 weeks for treatment not related to the drug treatment

Conclusions

- **Clinical activity was observed in heavily pretreated ET, PV, and MDS/MPN patients, including patients with JAK2, CALR, and MPL-mutated disease**
- **Meaningful platelet reductions were observed across all dose levels, with several patients achieving substantial and durable decreases from elevated baseline platelet counts.**
- **Platelet responses were tunable with dose adjustments**
- **JBI-802 demonstrated a manageable safety profile.**
- **Enrollment and dose escalation are ongoing, with additional efficacy, safety, and molecular response data expected from continued follow-up.**

References

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