Anti-tumor activity of CoREST inhibitor, JBI-802 (dual epigenetic modifier of LSD1/HDAC6): An opportunity to treat essential thrombocythemia and MPN/MDS patients with thrombocytosis in ongoing phase 1/2 clinical trial

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STUDY TITLE

- Study to Assess Safety and Preliminary Efficacy of Orally Administered JBI-802 in Subjects with Myeloproliferative Neoplasms (MPN) and Myelodysplastic/ Myeloproliferative Neoplasms (MDS/MPN) with Thrombocytosis.

BACKGROUND

- Myeloproliferative Neoplasms (MPN) are blood cancers originating from mutations in stem cells in the bone marrow, leading to the overproduction of white cells, red cells and platelets.
- Essential Thrombocythemia (ET) is a chronic MPN characterized by increased platelets, commonly diagnosed in individuals over 50, which can lead to blood clotting or bleeding and potentially transform into myelofibrosis or acute leukemia[1].
- Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) are clonal myeloid disorders with both dysplastic and proliferative features and unclassifiable MDS/MPN[1].
- Polycythemia Vera (PV) is another chronic MPN with increased red blood cell mass, leading to hyperviscosity and thrombosis, most common in patients over 60 years of age[2].
- JBI-802 is an orally active, highly potent, and selective dual LSD1/HDAC6 inhibitor developed by Jubilant Therapeutics which has shown promising results in pre-clinical studies including safety, and toxicology.
- A first-in-human study was initiated in 2022 for patients with advanced solid tumors and the initial dose of 10mg was found to be safe, though some patients at the highest dose experienced thrombocytopenia providing sufficient data for further clinical evaluations.
- Dose-dependent decrease in platelets as a part of MOA of LSD1 and HDAC6 inhibition provided an opportunity to treat patients with hematological malignancies like ET, MPN and MDS/MPN characterized by thrombocytosis.
- Jubilant Therapeutics Inc. has planned phase 1/2 study with the starting dose of 5mg, administered daily that was shown to be safe without major effect on platelets

OBJECTIVE

PART1: Dose Escalation Phase

Primary Objective:

To determine the Recommended Phase 2 Dose (RP2D) of JBI-802 in subjects with:

- MPN (ET, PV with thrombocythemia, Pre-fibrotic MF with thrombocythemia)
- MDS/MPN neoplasms (MDS/MPN-RS-T, MDS/MPN unclassifiable)

Secondary Objective:

- Evaluate the overall safety and tolerability of JBI-802.
- Assess the pharmacokinetic (PK) profile of JBI-802 and its metabolites
- Analyse the pharmacodynamics profile to assess drug effects.

PART2: Dose Expansion Phase

Primary Objective:

- To evaluate preliminary evidence of efficacy at the RP2D in subjects with:
- MPN (ET, PV and prefibrotic MF).
- MDS/MPN (MDS/MPN-RS-T, MDS/MPN unclassifiable and CMML subjects).

Secondary Objective:

- To further evaluate the overall safety and tolerability of JBI-802 as a single agent at the RP2D

STUDY OVERVIEW

- P1/2 — Phase 1/2
- Open labelled
- Geography - Australia
- Multi-Centric
- 30 patients for enrollment
- ACTRN12624000478516 — First patient dosed at Q3 2024

PATIENT INCLUSION / EXCLUSION CRITERIA

Key Inclusion Criteria:

- Age: Male or female subjects aged 18 years or older at the time of screening.
- Subjects must have one of the following diagnoses

For Dose Escalation Phase:

- Essential Thrombocythemia (ET) as per WHO criteria.
- Need for treatment to lower platelet count due to age over 60 or history of thrombosis.
- Morphologically confirmed diagnosis of MDS/MPN neoplasms (excluding JMML, CMML, and aCML) as per WHO 2016 revised criteria that are relapsed, refractory, or intolerant to standard care, with no available therapies providing clinical benefits.
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-UC) and MDS/MPN-RS-T.

For Dose Expansion Phase:

- Conditions: ET, PV, pre-fibrotic MF, MDS/MPN.
- Therapy History: Failed/intolerant to standard therapy.
- Prior Therapy: Stopped 1-4 weeks before study.
- Laboratory Values: Meet specific criteria for blood counts, Liver and kidney function
- Toxic effects: Resolved to Grade 0 or 1 according to NCI CTCAE, Version 5.0
- ECOG status: ≤ 2.
- Medication: Able to swallow oral medication.
- Consent: Willing to give informed consent and comply with protocol requirements.
- Biopsy: Willing to undergo bone marrow biopsy and tissue collection.
- Contraception: Willing to use effective contraception if needed.

Key exclusion criteria:

History of treatments with:

- systemic anticancer, biological therapy, or an investigational agent within 2 weeks or 5 half-lives before the study drug
- Underwent autologous/allogeneic HSCT within 60 days of the first dose, or on immunosuppressive therapy post-HSCT, or with significant GVHD.
- major surgery within 21 days prior to study drug or condition affecting medicine absorption.
- Underwent radiotherapy within 2 weeks before the study drug

CMML, chronic myelomonocytic leukemia; aCML atypical chronic myeloid leukemia; JMML, juvenile myelomonocytic leukemia ; PV, Polycythaemia vera; MF, Myelofibrosis; CTCAE, Common Terminology Criteria for Adverse Events; HCST, Hematopoietic stem cell transplantation; GVHD, Graft-versus-host disease

STUDY DESIGN (Part1- Dose Escalation)

- 3+3 study design
- Starting dose 5mg/day for 28 days

Dose Escalation (Cohort 1) → Dose Escalation (Cohort 2) → Dose Escalation (Cohort 3) → Dose Escalation (**Cohort X**) → RP2D/MTD

Initial dose escalation in subjects with:

- MPN (ET, PV with thrombocythemia, pre-fibrotic MF with thrombocythemia)
- MPN/MDS Neoplasms
- Baseline platelet count: ≥ 450 x 10^9/L

PART 2: Expansion Phase Cohorts in

- MPN: ET, PV, MF
- MDS/MPN): MDS/MPN-RS-T
- MDS/MPN unclassified
- CMML

Screening

- Performed with in 21 days prior to study drug administration

Treatment

Continue treatment until :

- Disease progression,
- Unacceptable toxicity or
- Maximum treatment cycles

Discontinue If :

- Consent withdrawal,
- Other Protocol criteria met

Safety Follow-up

- Follow up is done 28 days after the last dose
- Survival follow up phase is done for every 3 months

Once RP2D is determined proceed with PART 2 (Dose expansion).

To confirm Safety and preliminary efficacy of this dose in an expanded population of subjects

MPN, Myeloproliferative neoplasms; ET, Essential thrombocythemia ; PV, Polycythemia vera; MF, Pre-fibrotic myelofibrosis; MDS/MPN, Myelodysplastic/myeloproliferative neoplasms; CMML, Chronic myelomonocytic leukemia; MDS/MPN-RS-T, MDS/MPN with ring sideroblasts and thrombocytosis

STUDY ENDPOINTS

PRIMARY ENDPOINTS:

- DLT Events: Baseline to Day 28 of Cycle 1.
- Primary endpoints are ORR, DOR, CR and PFS: Investigator-assessed, MPN IWG–MRT and MDS/MPN IWG criteria (up to 2 years).
- Platelet Count reduction: ≤ 400×10^9/L without thromboembolic events (up to 2 years).
- Response Assessments based on: Spleen size ,Haematology and Bone marrow aspiration/biopsy evaluation.

SECONDARY ENDPOINTS:

- Adverse Events (AE): Types of AE and their seriousness, treatment relationship, timing, severity (NCI CTCAE V5.0) - up to 2 years.
- Clinical Changes examination for up to 2 years.
- Platelet Count reduction: ≤ 400×10^9/L without thromboembolic events (up to 2 years).
- Pharmacokinetic (PK) profile and Pharmacodynamic (PD) measurement
- Mutations: JAK2V617F, CALR, MPL proportions change from baseline

EXPLORATORY ENDPOINTS:

- Assessment of inflammatory cytokines

Efficacy

Safety

- Adverse event monitoring (NCI CTCAE V5.0) - up to 2 years
- Physical exams
- Vital sign measurements
- Electrocardiogram variables
- Hematology and chemistry

PK/PD

- PK and PD sampling: collected at specified time points

–Assessed Individual plasma concentration of JBI-802 with PK parameters such as Cmax, tmax, AUC and t½ .

–Change from baseline of CD11b and Acetyl-alpha-Tubulin (Cycle 1 Day 1, 8, 15; Cycle 2 Day 1) are assessed as PD measure

Biomarker

- Biospecimens (whole blood, plasma, bone marrow aspirate and/or bone marrow biopsy) analyses:
  - –Mutational status
  - –Bone marrow Analysis/profiling
  - –Inflammatory cytokines

REFERENCES

1.Mario Cazzola; Introduction to a review series on classic myeloproliferative neoplasms. *Blood* 2023; 141 (16): 1897–1899.

2.Tefferi A. Polycythemia vera: a comprehensive review and clinical recommendations. Mayo Clin Proc 2003; 78:174-94.

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SUMMARY

- We describe a Phase 1/2 trial (ACTRN12624000478516) investigating the safety, tolerability, and preliminary efficacy of JBI-802 administered in patients to treat with MPN/ET and MPN/MDS
- The trial is currently open for enrollment in Australia and is recruiting patients as of April 2024

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