PHASE 1/2A STUDY TO EVALUATE SAFETY, PHARMACOKINETIC AND PHARMACODYNAMIC DOSE ESCALATION AND EXPANSION STUDY OF PXS-5505 IN PATIENTS WITH PRIMARY, POST-POLYCYTHEMIA VERA OR POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS

R BAKER[1], J BASKAR[2], B CHARLTON[2], G HOBBS[3], W JAROLIMEK[2], S LEE[4], L MASAROVA[5] and A WATSON[6]

1. Perth Blood Institute, Murdoch University, Perth, Australia; 2. Pharmaxis Ltd, Frenchs Forest, NSW, Australia; 3. Division of Medical Oncology, Massachusetts General Hospital, Boston, MA; 4. Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea; 5. Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX; 6. Liverpool Hospital, Sydney, NSW, Australia.

ASH 2022

Abstract #1716

For additional information please contact: Jana.Baskar@Pharmaxis.com.au

BACKGROUND

- JAK inhibitors for myelofibrosis (MF) treatment provide major clinical benefits but can be significantly myelosuppressive and demonstrate modest effects on bone marrow fibrosis (BMF)
- High discontinuation rates are observed due to loss of therapeutic effect or drug induced toxicity
- The prognosis after ruxolitinib discontinuation is extremely poor with a median overall survival of only 11-14 months[1]
- Reducing BMF may normalize the hematopoietic environment resulting in stable or improved blood counts and also improve symptoms of MF
- Limited therapeutic options highlight the need for novel, effective therapies for MF

PXS-5505

- Lysyl oxidases (LOX) are a family of enzymes responsible for the critical post-translational modification essential for the biogenesis of cross-linked collagen and elastin, which form the basis of reticulin in bone marrow
- Tissue stiffening due to increases in collagen and number of cross-links (which is a hallmark of fibrosis), is preventable through LOX inhibition (Figure 1)
- All members of the LOX gene family are upregulated in MF providing a compelling rationale to therapeutically inhibit all LOX[2]
- Strong pre-clinical evidence demonstrated in a GATA-1 low murine model[3]

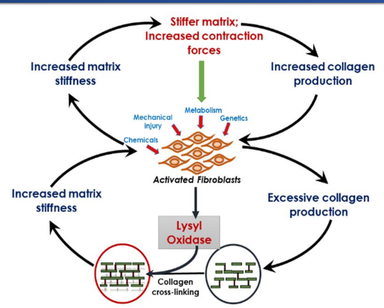


Figure 1: Lysyl oxidases contribute to the final stage in fibrosis

PXS-5505 is a pan-LOX inhibitor that prevents the cross-linking of collagen and elastin and consequently exhibits anti-fibrotic effects in murine models of MF

AIMS

- Ongoing, multi-center, open-label phase 1/2a study in patients with primary, post-polycythemia vera (PV) or post-essential thrombocythemia (ET) myelofibrosis (NCT04676529)
- Primary Objectives:
  - determine safety and tolerability of PXS-5505
- Secondary Objectives:
  - determination of appropriate dose
  - PK and PD
  - changes in BMF using European Consensus
  - spleen volume
  - MF symptoms (MFSAF)
- Study design and preliminary data from this study are presented here

METHODS

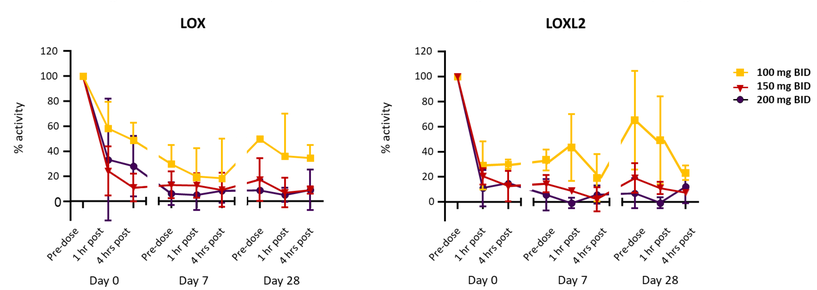
- The study consists of two phases: **Dose Escalation Phase (DEP)** and **Cohort Expansion Phase (CEP)**
- Patients must have PMF or post-ET/PV MF of intermediate/high risk; be relapsed/refractory, intolerant or ineligible to available JAK inhibitors and requiring therapy for symptomatic disease
- No exclusion of patients with severe thrombocytopenia
- The DEP had a 3+3 design, starting dose of 100 mg PXS-5505 BID for 4 weeks, escalating to 150 mg BID and to 200 mg BID. The DEP was to determine the maximum tolerated dose (MTD) or if all doses were well tolerated, the dose which provided the highest target engagement
- PK and PD measures during DEP included C_{min}, C_{max} and LOX/LOXL2 inhibition in plasma
- During the CEP, 24 patients will be treated at the dose determined from the DEP phase
- At data cutoff (30 September 2022) the DEP was completed and enrollment for the CEP continues

RESULTS – DEP

Dose Escalation Phase

- 5 patients were enrolled in the DEP; 4 pts with post ET MF, 1 pt with post PV MF
- Median age 71 years (range, 60-77), all female
- No suspected unexpected serious adverse reactions (SUSAR) or dose limiting toxicities during the DEP
- 1 pt terminated early following transformation to AML (24 days post treatment initiation)
- Majority (80%) AEs were mild, none were severe
- PK data from the DEP phase demonstrated that PK properties in patients were similar to PK in healthy volunteers (ACTRN12619000332123) at all dose levels
- At the 200mg BID level the mean trough LOX inhibition in plasma was 94% and 91% (days 7 and 28), respectively (Figure 2)
- Similarly, the mean trough LOXL2 inhibition in plasma was 94% and 93% (days 7 and 28 respectively)

Figure 2: >90% inhibition of LOX and LOXL2 in plasma on highest dose at day 7 and 28 (trough)



At 200mg BD dose level:
Mean LOX inhibition (trough): Day 7 - 94%; Day 28 - 91%
Mean LOXL2 inhibition (trough): Day 7 - 94%; Day 28 - 93%
*200mg BID dose selected for Cohort Expansion Phase

RESULTS - CEP

Cohort Expansion Phase

- As of 30 September 2022, 15 patients have been enrolled in the CEP with 6 patients having completed 24 weeks of treatment (Table 1)
- 4 patients have dropped out of the study due to a lack of clinical benefit
- PXS-5505 has been well tolerated with no serious treatment related adverse events reported
- Majority of AEs were mild (23/35 ≤ Grade 2)
- 85% of AEs were considered not treatment related
- No withdrawals due to AEs
- Of the 6 patients who have completed the 24 week CEP:
  - 2 had an improvement from baseline in MF-SAF TSS of ≥40% at 24 weeks
  - 5 had stable or improved bone marrow fibrosis scores of ≥1 grade as assessed by local hematopathology
  - 5 had stable/improved hemoglobin counts including one patient that had an anemia response (Hgb increase >20 g/L) at week 18 with no RBC transfusions (Figure 3)
  - 5 had stable/improved platelet counts over 24 weeks therapy (Figure 4)
- No reductions were seen in spleen volume as per IWG consensus criteria

Table 1: Demographics of patients completing CEP

Gender	Age	Disease duration (years)	RUX duration (months)	Time from last RUX dose to first dose PXS-5505 (days)
Female	72	12	8	41
Male	74	18	8	288
Female	71	8	55	15
Male	64	10	109	14
Male	86	1	N/A	N/A
Male	70	4	28	14

Figure 3: Hemoglobin (g/L) counts in patients completing CEP by study visit

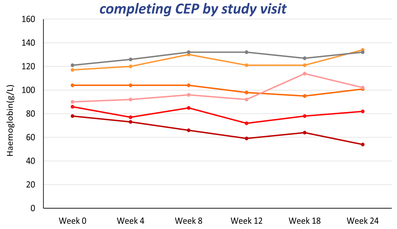
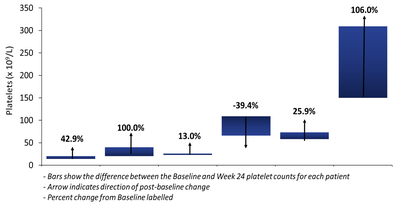


Figure 4: Platelet counts – Change from Baseline at Week 24 (by patient)



CONCLUSIONS

- All members of the lysyl oxidase gene family are upregulated in MF
- PXS-5505 is a pan-LOX inhibitor that prevents the cross-linking of collagen and elastin and, consequently, exhibits anti-fibrotic and anti-carcinogenic activities as seen in previous animal models
- This current study demonstrates that excellent targeted LOX and LOXL2 inhibition is being achieved at the 200mg BID level which has been selected as the recommended dose for the currently ongoing CEP
- PXS-5505 is well tolerated and the clinical responses support the continued investigation of PXS-5505 in MF with no dose limiting toxicity seen and preliminary indication of disease stabilisation
- Results are encouraging given the poor prognosis seen after ruxolitinib discontinuation with a median overall survival of only 11-14 months typical of this study population
- Results support further the continued clinical investigation of PXS-5505 in MF

PXS-5505 demonstrates >90% inhibition of lysyl oxidases at trough and is well tolerated

References: [1] Vachhani P., et al. J Clin Oncol. 2022; [2] Tadmor T., et al.. Am J Hematol. 2013; [3]Leiva O., et al. Int J Hematol. 2019