A phase I/IIa trial of PXS-5505, a novel pan-lysyl oxidase inhibitor, in advanced myelofibrosis

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Supplemental Table 1: Trial Objectives and Purpose

Primary Objective(s) The primary objective was to determine the safety and tolerability of PXS-5505 in patients with myelofibrosis (MF).
Secondary objectives Secondary objectives included: 1. Determining the appropriate therapeutic dose of PXS-5505 in patients with MF. 2. Characterizing the pharmacokinetic and pharmacodynamic parameters of PXS-5505 in patients with MF. 3. Determining reduction in bone marrow fibrosis in patients with MF administered PXS-5505 (European consensus grading). 4. Determining response rates as defined by the International Working Group (IWG) - Myeloproliferative Neoplasms Research and Treatment criteria in patients with MF administered PXS-5505. 5. Determining changes in spleen volume, as measured by computed tomography (CT) or magnetic resonance imaging (MRI) scan, in patients with MF administered PXS-5505. 6. Determining changes in MF related symptoms based on MFSAF v4.0 scores (Myelofibrosis Symptom Assessment Form v4.0 – 7-day recall), in patients with MF administered PXS-5505.
Exploratory objectives Exploratory objectives included to: 1. Evaluate the effect of PXS-5505 on markers of collagen and bone turnover. 2. Evaluate the effect of PXS-5505 on osteosclerosis and bone marrow (BM) fibrosis (by MRI). 3. Explore the correlations between biomarkers of disease burden (variant allele frequency [VAF] of driver mutation and high-molecular risk (HMR) genes) and other endpoints. 4. Evaluate platelet response – defined as: a. A minimum 100% increase in platelet count and an absolute platelet count of at least 50 x 10^9/L (in patients with baseline platelet count below 50 x 10^9/L) b. An absolute increase of 50 x10^9/L (in patients with baseline platelet counts between 50 and 100 x 10^9/L) 5. Explore the impact of PXS-5505 on ruxolitinib dosing (add-on phase only).

Supplemental Table 2: Overview of Study Design

Study design
This is a multi-center, open-label phase 1/2a study evaluating the safety and tolerability of PXS-5505 in patients with primary, post-polycythemia vera (PV) or post-essential thrombocythemia (ET) myelofibrosis. The primary endpoint is the evaluation of safety and tolerability. The study consists of three phases: a dose escalation phase (DEP), a cohort expansion phase (CEP) and an add-on phase. The dose escalation phase followed a 3+3 design and commenced at 100 mg twice daily, escalating to 150 mg twice daily and then to 200 mg twice daily. The treatment duration was 4 weeks. Patients were able to participate in more than one dose level. During the cohort expansion phase, 24 patients (to obtain 21 patients with at least one month's exposure) were treated at the dose determined appropriate based on safety, pharmacokinetic and pharmacodynamic results from the dose escalation phase, for a period of up to 6 months. Patients from the dose escalation phase were able to participate in the cohort expansion phase. The dose being used in the add-on phase is the PXS-5505 dose used in the cohort expansion phase in addition to ruxolitinib for up to 12 months. Sixteen patients have been enrolled in this phase of the study. Recruitment to the add-on phase commenced after at least 16 patients had completed 1 month's treatment in the cohort expansion phase.
Study population
Patients with pathologically confirmed primary myelofibrosis or post-ET/PV myelofibrosis as per the World Health Organization (WHO) criteria.[1] Patients meeting all of the inclusion criteria but none of the exclusion criteria were invited to participate.
Duration of therapy
Dose escalation phase: Up to four weeks per dose. Cohort expansion phase: up to 24 weeks. This enabled a preliminary assessment of efficacy and also provided longer term safety and tolerability information. Add-on Phase: up to 52 weeks. To enable a preliminary assessment of efficacy and also provide longer term safety and tolerability information in combination with ruxolitinib.

Dosage and Administration

Study drug – Dose escalation

Supplemental Table 3: Cohort A - Dose Level 1 - 100 mg twice daily

Cohort A_1 Three patients (n=3) will receive PXS-5505 **100 mg** twice daily for a period of 4 weeks. **If: <u>No</u>** dose-limiting toxicity observed in any of the three patients; *and* the C_{max} < 4,853 ng/mL[1] in all three patients; **then** following SMC approval **escalate** to **Cohort B, Dose Level 2, 150 mg twice daily** (see Table 2). **Else if:** There is **<u>one</u>** dose-limiting toxicity observed in the three patients and C_{max} < 4,853 ng/mL[1] in all patients, **then** an additional three patients will receive PXS-5505 **100 mg** twice daily for a period of 4 weeks (**Cohort A_2**, see below). The patient with the dose-limiting toxicity is withdrawn. **Else if: <u>Two or more</u>** patients experience dose-limiting toxicities and/or $C_{max} \geq$ 4,853 ng/mL[1] in *any* patient, **then STOP. *No tolerated dose determined*.**
Cohort A_2 Three patients (n=3) will receive PXS-5505 100 mg twice daily for a period of 4 weeks. **If: <u>No</u>** dose-limiting toxicity observed in any of the three patients; *and* the C_{max} < 4,853 ng/mL[1] in all three patients; **then** following SMC approval this cohort of patients will enter **Cohort B, Dose Level 2, 150 mg** twice daily (see Table 2). **Else if: <u>One</u>** or more patients experience dose-limiting toxicities (giving 2 or more out of 6 patients with dose-limiting toxicities at this dose overall) and/or $C_{max} \geq$ 4,853 ng/mL[1] in *any* patient **then: STOP. *No tolerated dose determined*.**

[1] Lowest C_{max} observed in 26-week toxicology studies at NOAEL of the most sensitive species.

Supplemental Table 4: Cohort B - Dose Level 2 - 150 mg twice daily

Cohort B_1 Three patients (n=3) will receive PXS-5505 150 mg twice daily for a period of 4 weeks (**Cohort B_1**). *Note: patients in this cohort may be the same as those recruited for one of the 100 mg twice daily cohorts A_1 or A_2.*# **If: <u>No</u>** dose-limiting toxicity observed in any of the three patients; *and* the C_{max} < 4,853 ng/mL[1] in all three patients **then** following SMC approval **escalate** to **Cohort C, Dose Level 3, 200 mg twice daily** (see Table 3). **Else if:** There is **<u>one</u>** dose-limiting toxicity observed in the three patients and the C_{max} < 4,853 ng/mL[1] in all patients, **then** an additional three patients will receive PXS-5505 150 mg twice daily for a period of 4 weeks (**Cohort B_2**, see below). The patient with the dose-limiting toxicity is withdrawn. **Else if: <u>Two or more</u>** dose-limiting toxicity observed in any of the three patients; *or* the C_{max} ≥ 4,853 ng/mL[1] in *any* of the three patients **then:** following SMC approval **CONTINUE to CEP, *100 mg twice daily determined as the MTD.***
Cohort B_2 Three patients (n=3) will receive PXS-5505 150 mg twice daily for a period of 4 weeks. *Note: patients in this cohort may be the same as those recruited for one of the 100 mg cohorts A_1 or A_2* # *but must not include subjects recruited into B_1.* **If: <u>No</u>** dose-limiting toxicity observed in any of the three patients; *and* the C_{max} < 4,853 ng/mL[1] in all three patients; **then** following SMC approval this cohort of patients will enter **Cohort C, Dose Level 3, 200 mg** twice daily (see Table 3). **Else if: <u>One</u>** or more patients experience dose-limiting toxicities (giving 2 or more out of 6 patients with dose-limiting toxicities at this dose overall) and/or C_{max} ≥ 4,853 ng/mL[1] in *any* patient **then:** following SMC approval **CONTINUE to CEP, *100 mg twice daily determined as the MTD.***

[1]Lowest C_{max} observed in 26-week toxicology studies at NOAEL of the most sensitive species.
Patients treated at more than one dose level during dose escalation must repeat Visits 1, 2, 3 and follow-up (telephone) 1 week post study drug discontinuation for each dose level.

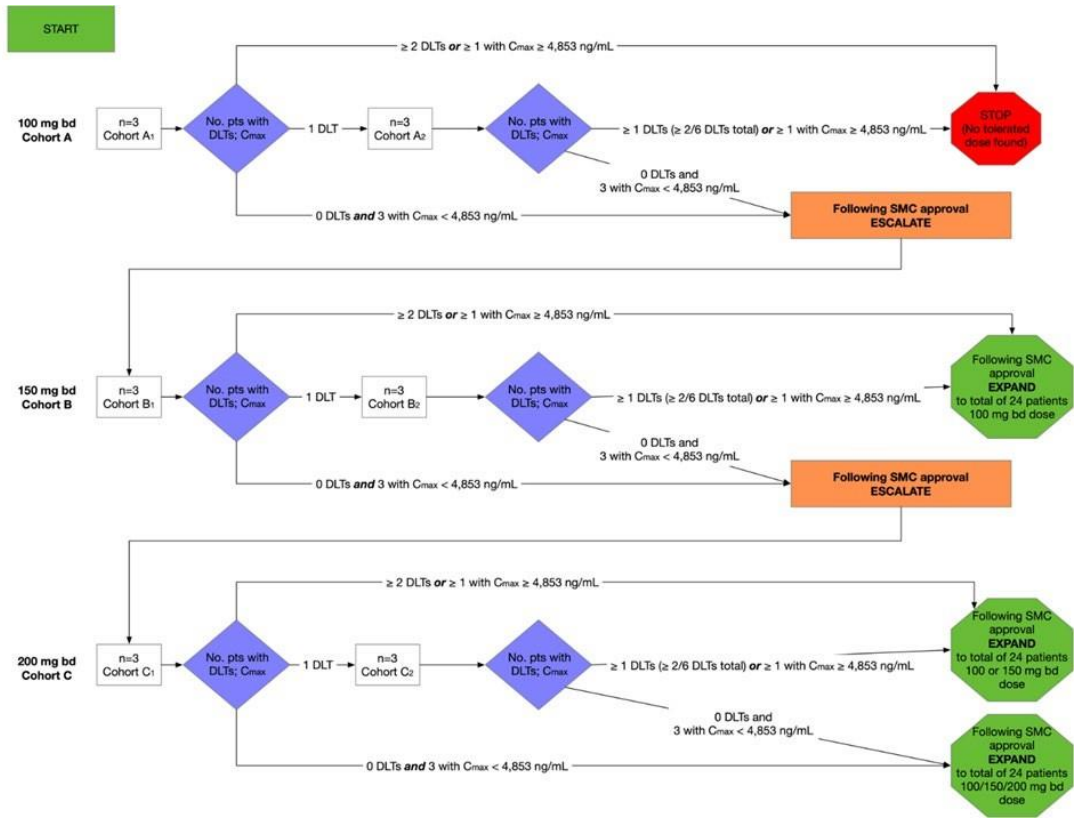
Supplemental Table 5: Cohort C - Dose Level 3 - 200 mg twice daily

Cohort C_1 Three patients (n=3) will receive PXS-5505 200 mg twice daily for a period of 4 weeks (**Cohort C_1**). *Note: patients in this cohort may be the same as those recruited for one of the 100 mg or 150 mg cohorts A_1, A_2, B_1 or B_2.*[#] **If: <u>No</u>** dose-limiting toxicity observed in any of the three patients; *and* the C_{max} < 4,853 ng/mL[1] in all three patients **then** following SMC approval **CONTINUE to CEP, *at 200 mg twice daily, no MTD determined*.** **Else if:** There is **<u>one</u>** dose-limiting toxicity observed in the three patients and the C_{max} < 4,853 ng/mL[1] in all patients, **then** an additional three patients will receive PXS-5505 200 mg twice daily for a period of 4 weeks (**Cohort C_2**, see below). The patient with the dose-limiting toxicity is withdrawn. **Else if: <u>Two or more</u>** dose-limiting toxicity observed in any of the three patients; *or* the C_{max} ≥ 4,853 ng/mL[1] in *any* of the three patients; following SMC approval **CONTINUE to CEP, *150 mg twice daily determined as the MTD.***
Cohort C_2 Three patients (n=3) will receive PXS-5505 200 mg twice daily for a period of 4 weeks. *Note: patients in this cohort may be the same as those recruited for one of the 100 mg twice daily or 150 mg twice daily cohorts A_1, A_2, B_1 or B_2.*[#] *but must not include subjects recruited into C_1.* **If: <u>No</u>** dose-limiting toxicity observed in any of the three patients; *and* the C_{max} < 4,853 ng/mL[Error! Bookmark not defined.] in all three patients; following SMC approval **CONTINUE to CEP, *at 200 mg twice daily, no MTD determined.*** **Else if: <u>One</u>** or more patients experience dose-limiting toxicities (giving 2 or more out of 6 patients with dose-limiting toxicities at this dose overall) and/or C_{max} ≥ 4,853 ng/mL[1] in *any* patient then**:** following SMC approval **CONTINUE to CEP, *150 mg twice daily determined as the MTD.***

[1]Lowest C_{max} observed in 26-week toxicology studies at NOAEL of the most sensitive species.
Patients treated at more than one dose level during dose escalation must repeat Visits 1, 2, 3 and follow-up (telephone) 1 week post study drug discontinuation for each dose level.

Dose escalation proceeded until either ≥ 2 dose-limiting toxicities were recorded, ≥ 1 patient had a C_{max} ≥ 4,853 ng/mL or the highest planned dose was reached. Dose escalation commenced using PXS-5505 100 mg twice daily, with escalations to 150 mg twice daily, and then to 200 mg twice daily with up to 4-weeks treatment duration per dose.

Supplemental Figure 1: 3+3 Design For Dose Escalation Phase (Excerpt from Protocol)



Supplemental Table 6: Study drug – Cohort Expansion Phase

Following review of the data (safety, pharmacokinetic (PK) and pharmacodynamic (PD)) from the DEP the decision to proceed into the CEP, and at what dose level, was made by the Safety Monitoring Committee (SMC). Up to 24 additional patients were recruited. All patients received PXS-5505 at the selected twice daily dose for a period of 24 weeks, or until progressive disease, unacceptable toxicity, DLT or withdrawal of consent. Patients from the dose escalation cohorts were able to participate in the CEP. If they continued into the CEP within 35 days of their last treatment in the DEP then there was no need to repeat Visit 0 (screening). However, a bone marrow biopsy needed to have been performed within six months of their re-initiation of treatment with PXS-5505 in the DEP, otherwise it had to be repeated.

Supplemental Table 7: Time and Events Schedule – Dose Escalation Phase

Sourced from PXS5505-MF-101 Study Protocol V8.1

Event	Screening[1] Visit 0	Visit 1 Baseline	Visit 2	Visit 3	Follow-up - Telephone	Follow-up/Discharge Visit
Visit week	-2 weeks	Week 0	Week 1	Week 4	1 week post Tx discontinuation	4-week post Tx discontinuation
Visit due at day (± visit window)	Day -14 to Day -1	Day 0	Day 7 ± 1 day	Day 28 ± 1 day	7 days ± 1 day post-Tx discontinuation	28 days -1 to + 7 days post-Tx discontinuation
Informed consent[2]	X					
Inclusion/exclusion criteria[3]	X					
Pregnancy testing[4]	X	X	X	X		X
Demographics[5]	X					
Medical history[6]	X					
Recent surgical, injury history & blood transfusion history[7]	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Physical examination/ vital signs	X	X	X	X		X
Adverse Event/serious adverse event assessment		X	X	X	X	X
Dose-limiting toxicity (DLT)		X	X	X	X	X
12-lead ECG[8]		X	X	X		
Spleen volume assessment[9]		X				
Clinical laboratory tests[10]	X	X	X	X		X
Symptoms assessment (MFSAF v4.0 7-day recall)	X					
Dispense study drug		X	X			
Drug compliance and accountability[11]			X	X		
Pharmacokinetic (PK) blood sample[12]		X	X	X		
Pharmacodynamic (PD) blood sample[13]		X	X	X		
Discharge subject from study						X

[1] Note if patients enter more than one dose level during dose escalation or continue into cohort expansion, they complete all visits up to and including Follow up (Telephone) at their initial dose level and then commence the next dose level or cohort expansion at Visit 1 if ≤ 35 days since last dose ie. they do not need re-screening. If > 35 days since last dose they will be required to complete Follow up/discharge visit – 4 week post study drug discontinuation and then be rescreened and allocated a new subject number prior to escalating doses or entering cohort expansion.
[2] Consent must be obtained before any protocol procedures being performed
[3] Pathologically confirmed diagnosis of PMF or post-ET/PV MF as per the WHO 2016 diagnostic criteria (note that it must include at least Grade 2 marrow fibrosis).
[4] Serum and urine pregnancy testing for women of childbearing potential only.
[5] Age, sex, body mass index.
[6] Including MF type (PMF, Post-PV or Post-ET), disease duration, concomitant diseases and full medical history and ECOG status.
[7] Blood transfusion history for 12 weeks prior to screening visit.
[8] ECGs will be performed up to 60 minutes prior to study drug administration, in triplicate. Clinically significant abnormal results will be reported as adverse events.
[9] Via MRI or CT (same method to be used throughout trial for a given patient) up to 6 wks prior to baseline (Visit 1). It does not need to be repeated if patient participates in subsequent dose level cohorts.
[10] Hematology/Immunopathology: full blood count, beta-2 microglobulin, serum free light chains (Kappa/Lambda ratio), immunoelectrophoresis; Clinical chemistry: electrolytes including calcium, magnesium and phosphate creatinine, lactic dehydrogenase, troponin 1; Liver function: direct bilirubin, total bilirubin, albumin, total protein, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase and alkaline phosphatase; Kidney function: serum creatinine, blood urea nitrogen, estimated glomerular filtration rate; urinalysis; Bone metabolism: PTH, calcitonin, vitamin D (Bone metabolism not performed at screening); Heart Function: BNP (not performed at screening).
[11] Also to be collected at withdrawal if patient withdraws between scheduled visits.
[12] The dose taken prior to PK blood sampling must be taken under supervision. PK blood sample to be collected at t=0 (pre-dose), 1 h (± 5 mins), and 4 h (±15 mins) post-dose for assessment of C_{1hr}=C_{max} and $C_{min.}$
[13] The dose taken prior to PD blood sampling must be taken under supervision. PD sampling at t=0 (pre-dose), 1 h (± 5 mins), and 4 h (± 15 mins), post-dose to assess LOX & LOXL2 inhibition in plasma.

Supplemental Table 8: Time and Events Schedule – Cohort Expansion Phase

Sourced from PXS5505-MF-101 Study Protocol V8.1

Event	Screening Visit 0	Visit 1[1] Baseline	Visit 2	Visit 3	Telephone Visit	Visit 4	Visit 5	Visit 6	Follow-up
Visit week	Week -2	Week 0	Week 1	Week 4	Week 8	Week 12	Week 18	Week 24	4 weeks post Tx discontinuation
Visit due at day (± visit window)	Day -14 to Day -1	Day 0	Day 7 ± 1 day	Day 28 ± 1 day	Day 56 ± 1 day	Day 84 ± 3 days	Day 126 ± 3 days	Day 168 ± 3 days	28 ± 3 days post-Tx discontinuation
Informed consent[2]	X	(X)[3]							
Inclusion/exclusion criteria	X								
Pregnancy testing[4]	X	X	X	X		X	X	X	X
Demographics[5]	X								
Medical history[6]	X								
Recent surgical, injury history, & blood transfusion history[7]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X		X	X	X	X
Physical examination/ vital signs	X	X	X	X		X	X	X	X
Adverse event / serious adverse event/DLT assessment		X	X	X	X	X	X	X	X
12-lead ECG[8]		X	X	X		X	X	X	
Clinical laboratory tests[9]	X	X	X	X		X	X	X	X
Bone marrow biopsy/bone marrow assessment		X[10]				X		X	
Response rates (IWG-MRT criteria)						X		X	
Spleen volume assessment[11]		X				X		X	
Symptoms assessment (MFSAF v4.0 7-day recall)	X	(X)[12]				X		X	
Bone collagen marker blood & urine sample[13]		X				X		X	
Femur MRI		X[14]				X		X	
Dispense study drug		X	X	X		X	X		

Event	Screening Visit 0	Visit 1[1] Baseline	Visit 2	Visit 3	Telephone Visit	Visit 4	Visit 5	Visit 6	Follow-up
Visit week	Week -2	Week 0	Week 1	Week 4	Week 8	Week 12	Week 18	Week 24	4 weeks post Tx discontinuation
Visit due at day (± visit window)	Day -14 to Day -1	Day 0	Day 7 ± 1 day	Day 28 ± 1 day	Day 56 ± 1 day	Day 84 ± 3 days	Day 126 ± 3 days	Day 168 ± 3 days	28 ± 3 days post-Tx discontinuation
Drug compliance and accountability[15]			X	X		X	X	X	
PK blood sample[16] PD blood sample[17]		X		X		X		X	
Peripheral blood sample for biomarkers of disease burden[18]		X[19]				X[19]		X[19]	
Discharge subject from study								X[20]	X[20]

[1] Note if patient has participated in the DEP and their last dose was ≤ 35 days, then Visit 0 (screening) is not required and the patient will commence the new cohort at Visit 1. If the patient participated in the DEP and had last dose > 35 days ago, they commence at Visit 0 (screening).
[2] Consent may be obtained before screening visit but MUST be obtained prior to any protocol procedures being performed.
[3] If patient did not have a screening visit.
[4] Serum and urine pregnancy testing for women of childbearing potential only.
[5] Age, sex, body mass index.
[6] Including MF type (PMF, Post-PV or Post-ET), disease duration, concomitant diseases and full medical history and ECOG PS.
[7] Blood transfusion history for 12 weeks prior to screening visit.
[8] ECGs will be performed up to 60 minutes prior to study drug administration, in triplicate. Clinically significant abnormal results will be reported as adverse events.
[9] Hematology/Immunopathology: full blood count, beta-2 microglobulin, serum free light chains (Kappa/Lambda ratio*)*, immunoelectrophoresis; Clinical chemistry: electrolytes including calcium, magnesium and phosphate, creatinine, lactic dehydrogenase, troponin 1; Liver function: direct bilirubin, total bilirubin, albumin, total protein, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase and alkaline phosphatase; Kidney function: serum creatinine, blood urea nitrogen, estimated glomerular filtration rate; urinalysis; Bone metabolism: PTH, calcitonin, vitamin D (Bone metabolism not performed at screening); Heart Function: BNP (not performed at screening).
[10] Biopsy must be within 6 months of Visit 1 of the CEP to establish baseline fibrosis score for patients who participated in the DEP, or within 3 months of Visit 1 (ie first day of dosing) otherwise. Biopsy will be used for bone marrow assessment.
[11] Via MRI or CT (same method to be used throughout trial for a given patient) up to 6 wks prior to baseline (Visit 1).
[12] If patient participated in DEP and does not require screening (≤ 35 days since last dose of PXS-5505), the symptoms assessment may be completed at Visit 1
[13] Bone and Collagen turnover markers: alkaline phosphatase, osteocalcin, CTX, CTXIII, C3M, C4M, PRO-C3, urinary hydroxyproline
[14] Baseline MRI can be performed up to 14 days prior to Visit 1 (baseline).
[15] Also to be collected at withdrawal if subject prematurely withdraws between visits.
[16] The dose taken prior to PK blood sampling must be taken under supervision. PK blood sample to be collected at t=0 (pre-dose), 1 h (± 5 mins) and 4 h (± 15 mins) post-dose for assessment of C_{1hr}=C_{max} and $C_{min.}$

[17] The dose taken prior to PD blood sampling must be taken under supervision. PD sampling at t=0 (pre-dose), 1 h (± 5 mins), and 4 h (± 15 mins) post-dose to assess LOX & LOXL2 inhibition in plasma.
[18] DNA sample of peripheral blood stored at room temperature.
[19] If subject was recruited into the study prior to this peripheral blood sampling being required, any relevant biomarker information collected as part of subject's routine care from 3 months prior to Visit 1 is to be captured.
[20] If patient is continuing with PXS-5505 after Visit 6 eg. Named patient supply, then discharge from study is to be performed at Visit 6 and no follow-up visit is required.

Supplemental Table 9: Subject Inclusion Criteria

The subject must meet the following criteria:
1. Aged 18 years or older; 2. Had a pathologically confirmed established diagnosis of PMF or post-ET/PV MF as per the WHO 2016 diagnostic criteria (note it had to include at least Grade 2 marrow fibrosis); 3. Patients were not eligible for stem cell transplantation; 4. Patients were not on ruxolitinib or fedratinib treatment due to ineligibility, or previously treated patients had been discontinued for at least 2 weeks prior to first dose of study drug due to any of the following criteria: a. **Ineligible:** Platelets < 50 x 10^9/L b. **Intolerant:** Development of RBC transfusion dependence of at least two units/month for 2 months OR ≥ Grade 3 adverse events of thrombocytopenia, anemia, hematoma, and/or hemorrhage while on treatment with ruxolitinib or fedratinib for at least 28 days. c. **Refractory:** < 10% spleen volume reduction by MRI or CT, or < 30% decrease from baseline in spleen volume by palpation after at least 3 months treatment with ruxolitinib or fedratinib d. **Relapsed:** Regrowth to < 10% spleen volume reduction by MRI or CT, or < 30% decrease from baseline in spleen volume by palpation, following an initial response to ruxolitinib or fedratinib and after at least 3 months treatment. 5. Intermediate -2, or high-risk disease according to the IWG prognostic scoring system (DIPSS); 6. Symptomatic disease according to the MFSAF v4.0; Symptomatic disease defined as a score of at least one in at least two items of the MFSAF v4.0; 7. Life expectancy of six months or greater; 8. Must have had adequate organ function as demonstrated by the following (within last 2 weeks): a. ALT (SGPT) and/or AST (SGOT) ≤ 2.5x upper limit of normal (ULN), or ≤ 4 x ULN (if upon judgment of the treating physician, it is believed to be due to extramedullary hematopoiesis [EMH] related to MF); b. Direct bilirubin ≤ 1.5 x ULN; or ≤ 2 x ULN (if upon judgment of the treating physician, it is believed to be due to EMH related to MF); c. Estimated glomerular filtration rate (eGFR) > 50 mL/min 9. Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2; 10. Men must have agreed to using one medically approved (i.e., mechanical or pharmacological) contraceptive measure and had their partners agree to an additional barrier method of contraception for the duration of the study and for 90 days after the last administration of study drug; Women of childbearing potential had to use effective contraception. Adequate methods of contraception included use of oral contraceptives or Depo-Provera, with an additional barrier method (diaphragm with spermicidal gel or condoms with spermicide), double-barrier methods (diaphragm with spermicidal gel and condoms with spermicide), partner vasectomy, and total abstinence; 11. **[CEP only]** A bone marrow biopsy must have been performed within 3 months prior to Day 1 treatment to establish the baseline fibrosis score or within 6 months of the re-initiation of treatment with PXS-5505 if subject participated in DEP of the trial.

Supplemental Table 10: Subject Exclusion Criteria

The subject must NOT have had:
1. Greater than (>) 10% blasts in peripheral blood (determined within last two weeks); 2. Prior splenectomy, or planned to undergo splenectomy, or splenic irradiation within 3 months prior to the first dose of study treatment; 3. Any serious medical condition or psychiatric illness that would have prevented (as judged by the treating physician) the subject from signing the informed consent form or any condition, including the presence of laboratory abnormalities, which placed the subject at unacceptable risk if he/she had participated in the study or confounded the ability to interpret data from the study; 4. Known history of human immunodeficiency virus (HIV), active hepatitis C, or active hepatitis B; 5. History or presence of any form of cancer within the three years prior to enrolment, with the exception of excised basal cell or squamous cell carcinoma of the skin, or cervical carcinoma in situ or breast carcinoma in situ that had been excised or resected completely and was without evidence of local recurrence or metastasis; 6. Participated in an investigational drug or device trial within two weeks prior to study Day 1 or within five times the half-life of the investigational agent in the other clinical study, if known; 7. Used any cytotoxic chemotherapeutic agents, including hydroxyurea, corticosteroids (prednisone ≤ 10 mg/day or corticosteroid equivalent is allowed), or immune modulators (e.g., thalidomide) within two weeks and interferon use within four weeks prior to study Day 1; 8. Symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or unstable cardiac arrhythmia requiring medication; 9. Pregnancy; Note: A pregnancy test was performed for all females of child-bearing potential at all visits (expect the telephone visit) 10. History of surgery within two weeks prior to enrolment or anticipated surgery during the study period or two weeks post-study; 11. History of aneurysm; *or* 12. Any other condition that might have reduced the chance of obtaining data required by the protocol or that might have compromised the ability to give truly informed consent.

Supplemental Table 11: Statistical Methods

General considerations

Safety endpoints were assessed in all treated patients. Analysis of efficacy endpoints in the DEP / CEP were assessed in all treated patients and where applicable, also the completer population.

In general, continuous variables were summarized using the statistics: number of non- missing observations (N), mean, median, standard deviation (SD), minimum (Min) and maximum (Max), unless otherwise stated. Categorical variables were summarized with frequency counts and percentages, with the denominator being the number of subjects in the relevant population, unless otherwise stated.

For the PK and PD data, summary statistics also included the geometric mean and geometric coefficient of variation (CV) (%).

All data was summarized overall, and separately for each different dose level and separately for the expansion phase.

Note: patients who are entered in more than one cohort were included in the summaries of each cohort. Baseline was defined as the date of starting the dose in the relevant cohort.

Missing values

No imputation of missing data was planned.

Dropouts

All recorded data from subjects who discontinued have been reported to the point of study cessation.

Multiple comparisons

Not applicable.

Interim analysis

No formal interim analysis was planned.

Informal interim assessments of accumulating data were planned during the DEP to determine whether the dose was to be increased, and if progression to the CEP (and at which dose) could occur. Informal interim assessments of accumulating data were also planned during the CEP, so as to determine if progression to the add-on phase could occur. Informal interim assessments of accumulating data during the add-on phase will also occur. Data from the CEP may also be formally reported prior to the completion of the add-on phase.

Trial Stopping rules and dose reduction

Dose escalation: The Safety Monitoring Committee examined accumulated outcome and safety data every three months in order to make recommendations concerning continuation, termination or modification of the trial based on the effects of the interventions under trial. They were also involved in dose escalation decisions and in selection of the dose for the CEP.

If no dose had been found to be tolerable (that is, no dose has less than two patients out of six with dose-limiting toxicities with acceptable PK), then the trial would have been stopped.

Cohort expansion: The Safety Monitoring Committee examined accumulated outcome and safety data approximately every three months in order to make recommendations concerning continuation, termination or modification of the trial based on the effects of the interventions under trial. They were also involved in the decision to proceed to the add-on phase based on accumulating data from the CEP

Supplemental Table 12: Measurement of Lysyl Oxidase and Lysyl Oxidase-Like 2 Concentration and Activity

Lysyl oxidase (LOX) and lysyl oxidase-like 2 (LOXL2) concentrations were measured, as described previously,[2,3] for healthy and MF patients. Sample numbers: LOX concentration (healthy/disease n=30); LOXL2 concentration (healthy n=36; disease n=32). Healthy control samples came from two studies and an academic group with Dr Arantxa González Miqueo, Universidad de Navarra, Spain (LOXL2 only).[2] MF patients were from PXS5505-MF-101 (MF-101) DEP and CEP subjects, age range 60 to 86.

LOX and LOXL2 activities were measured, as described previously,[2,3] for healthy and MF patients. Sample numbers: LOX activity (healthy n=36; disease n=24); LOXL2 activity (healthy: 109; disease n=30). Healthy control samples came from PXS-5505 Single Ascending and Multiple Ascending Dose Study, age range 26 to 39 and PXS-5338/PXS-5382 SAD and MAD phase study age range 18 to 59 (LOXL2 only).[4] MF patients were from MF-101 DEP (LOXL2 only due to technical issues with the LOX assay) and CEP subjects, age range 60 to 86. Activities were measured in subjects at baseline (i.e. pre-dose).

Assay Methodology

The Simoa technology was described in the following reference: Rissin DM, Kan CW, Campbell TG, et al. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. Nat Biotech 2010; 28:595–99. [5]

Sample preparation: human plasma samples were diluted at least 6 fold in Assay Buffer (1% BSA, 0.25% Rabbit Serum, 2% PEG (20k MW), 0.55% Tween-20, 1x PBS). To determine the specific LOX activity, diluted samples were pre-incubated for 30 min with a pan-LOX inhibitor beta-aminoproprionitrile (BAPN). Controls were also diluted in assay buffer. The bioprobe (biotinylated detector) was diluted to 130 µM in deionized H2O.

The (L4794)-target-antibody-coated paramagnetic beads (500k per mL) were combined with diluted sample and biotinylated detector-bioprobe (1.2 µM) in the same incubation cuvette for 54 min. Target molecules present in the sample were captured by the antibody coated beads and bound with the biotinylated bioprobe simultaneously. Following a wash, a conjugate of streptavidin-β-galactosidase (SβG) at 150 pM was mixed with the beads and incubated for 5 min. SβG bound to the biotin moiety of bioprobe, resulting in enzyme labelling of captured target. Following a final wash, the beads were resuspended in a resorufin β-D-galactopyranoside (RGP) substrate solution and transferred to a Simoa Disc. Individual beads were then sealed within microwells in the array.

Once the target was captured and labelled on the bead, β-galactosidase hydrolysed the RGP substrate in the microwell into a fluorescent product that provided the signal for measurement. A single-labelled target molecule resulted in sufficient fluorescent signal and was detected and counted by the Simoa optical system. The average number of enzymes per bead (AEB) was calculated. At low target concentration, the AEB was proportional to the amount of target present in the sample. At higher target concentration, when most of the bead-containing wells had one or more labelled target molecules, the total fluorescence signal was proportional to the amount of target present in the sample.

Supplemental Table 13: Pharmacokinetic and Pharmacodynamic Assessments

Pharmacokinetic samples were collected as per the Time and Events Schedule. For single dose PK assessment, samples were collected at t=0 (pre-dose), 1 h (±5 mins), and 4 h (±15 mins) post-dose which allowed for assessment of C_{max} and C_{min}.

Pharmacodynamic samples were collected as per the Time and Events Schedule. For single dose PD assessment, samples were collected at t=0 (pre-dose), 1 h (±5 mins), and 4 h (±15 mins) post-dose which allowed for assessment of LOX and LOXL2 inhibition.

Not all patients continuing in the study at a particular timepoint had samples available for analysis at that timepoint (for example one patient had no pre-dose LOX or LOXL2 activity results at Day 168 due to a lost sample). In total, 3 patients had results excluded from one or more PK/PD endpoint for a variety of reasons, as detailed below:

PK - 2 patients had data excluded:

1. Patient A: All time-points at day 168 excluded due to lack of compliance
2. Patient B: All time-points at day 28, 84 and 168 excluded due to lack of compliance.

[Note Patient C would also have been excluded from PK analysis at Day 84 but had no results available due to hemolysed (pre-dose) and missing (1h, 4h) PK samples at this timepoint]

LOX activity - 3 patients had data excluded:

1. Patient A: All timepoints at day 0, day 28, day 84 and day 168 as the variability of the results at Day 0 exceeded acceptable levels (i.e. from 170% at 1 hour to-2% at 4 hours); likely a problem of the accuracy of measurement of the Day 0 pre-dose sample (therefore all later timepoints excluded as % activity calculated from this result).
2. Patient B: Pre-dose time-point at day 28, 84 and 168 excluded due to missed doses.
3. Patient C: Day 84 pre-dose data was excluded due to dose interruption/large dose gap (Day 168 activity normalized to pre-dose value at Day 84 rather than Day 0)

LOXL2 activity - 2 patients had data excluded:

1. Patient B: Pre-dose time-point at day 28, 84 and 168 excluded due to missed doses.
2. Patient C: All timepoints at day 0, 28, 84 and 168 excluded as % activity not calculated due to lower than acceptable Total activity (Signal/Noise) at Day 0 (likely analysis issue)

[Note: Patient A would also have had Day 168 pre-dose data excluded for missed doses but this sample was lost and not analysed]

PXS-5505 plasma concentrations were measured on days 0, 7 and 28 for the DEP and on days 0, 28, 84, and 168 for the CEP. Based on the DEP results, steady state was achieved by 28 days with the maximum concentration almost always observed at 1 hour post dosing. To calculate the average Cmax at steady state in the CEP, the mean across all 1-hour post-dose values at steady state (i.e. at days 28, 84 and 168) for each patient was calculated. The overall mean was then calculated as the average of the mean for each patient.

Supplemental Table 14: Spleen Volume Over Time (by patient)

Subject	Days from end of prior JAKi treatment to BL SV assessment	BL	W12	% Change from BL to W12	W24	% Change from W12 to W24	% Change from BL to W24
1	28	1084	1408	30%	1361	-3%	26%
2	>28	847	1005	19%	1122	12%	32%
3	12	1317	1342	2%	1565	17%	19%
4	6	4586	5038	10%	4145	-18%	-10%
5	No prior JAKi	820	813.6	-1%	Not Done	-	-
6	0	484	684	41%	664	-3%	37%
7	>28	1696	2928	73%	4303	47%	154%
8	0	530	892	68%	767	-14%	45%
9	21	2852	3067	8%	3401	11%	19%
10	15	3308	4432	34%	5513	24%	67%
11	>28	5647	5480	-3%	5505	0%	-3%
12	>28	2195	Not Done	-	2579	-	17%
13	>28	359	359	0%	366	2%	2%

SV: Spleen volume; BL: Baseline

Supplemental Table 15: Surgical Interventions and Study Outcomes

Subject	Phase	Surgery	Interruption in Study Drug?	Outcome	Subject Status
A	DEP (150mg bid)	Skin Lesion Removal	No	No AEs related to wound healing reported	**Completed 3 doses in DEP and CEP**
	CEP	Skin neoplasm excision	No	No AEs related to wound healing reported	
		Debridement	No	No AEs related to wound healing reported	
B	CEP	Inguinal hernia repair	Yes (14 days)	No AEs related to wound healing reported	**Completed CEP**
		Cardiac pacemaker and implantable defibrillator insertion	No	No AEs related to wound healing reported	
C	CEP	Abscess drainage	Yes (10 days)	No AEs related to wound healing reported	**Completed CEP**

Supplemental Table 16: Summary of adverse events regardless of study drug relationship by SOC/Preferred Term (Dose Escalation Phase)

	Dose escalation (N=5)					
SOC/Preferred Term, N (%) E	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
Blood and lymphatic system disorders			**1 (20) 1**			**1 (20) 1**
Anemia			1 (20) 1			1 (20) 1
Gastrointestinal disorders	**1 (20) 2**	**1 (20) 1**				**2 (40) 3**
Abdominal discomfort	1 (20) 1					1 (20) 1
Constipation		1 (20) 1				1 (20) 1
Nausea	1 (20) 1					1 (20) 1
General disorders and administration site conditions	**1 (20) 1**					**1 (20) 1**
Oedema peripheral	1 (20) 1					1 (20) 1
Injury, poisoning and procedural complications	**2 (40) 3**					**2 (40) 3**
Contusion	1 (20) 1					1 (20) 1
Transfusion reaction	1 (20) 1					1 (20) 1
Wound	1 (20) 1					1 (20) 1
Investigations	**1 (20) 1**			**1 (20) 1**		**2 (40) 2**
Platelet count decreased				1 (20) 1		1 (20) 1
Troponin increased	1 (20) 1					
Metabolism and nutrition disorders	**2 (40) 2**	**1 (20) 1**				**2 (40) 3**
Decreased appetite	1 (20) 1					1 (20) 1
Dehydration		1 (20) 1				1 (20) 1
Hyperuricaemia	1 (20) 1					1 (20) 1
Musculoskeletal and connective tissue disorders	**1 (20) 1**					**1 (20) 1**
Myalgia	1 (20) 1					1 (20) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (20) 1**				**1 (20) 1**	**2 (40) 2**
Squamous cell carcinoma of skin	1 (20) 1					1 (20) 1
Transformation to acute myeloid leukaemia					1 (20) 1	1 (20) 1
Nervous system disorders		**1 (20) 1**				**1 (20) 1**
Headache		1 (20) 1				1 (20) 1

Renal and urinary disorders	**1 (20) 1**					**1 (20) 1**
Renal impairment	1 (20) 1					1 (20) 1
Respiratory, thoracic and mediastinal disorders	**1 (20) 1**	**1 (20) 2**				**2 (40) 3**
Cough	1 (20) 1					1 (20) 1
Pleural disorder		1 (20) 1				1 (20) 1
Pulmonary mass		1 (20) 1				1 (20) 1
Skin and subcutaneous tissue disorders	**1 (20) 1**					**1 (20) 1**
Petechiae	1 (20) 1					1 (20) 1

Supplemental Table 17: Summary of adverse events regardless of study drug relationship by SOC/Preferred Term (Cohort Expansion Phase)

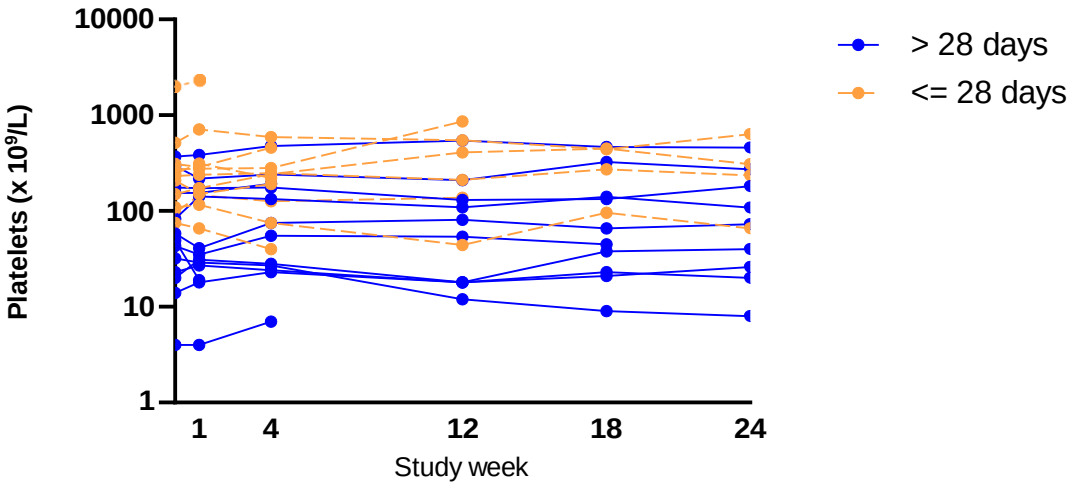
	Cohort Expansion (N=24)						
SOC/Preferred Term, N (%) E	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Unknown**	**Total**
Blood and lymphatic system disorders		**1 (4.2) 1**	**2 (8.3) 3**	**2 (8.3) 2**	**1 (4.2) 1**		**5 (20.8) 7**
Anaemia			1 (4.2) 1	1 (4.2) 1			2 (8.3) 2
Febrile neutropenia			1 (4.2) 2		1 (4.2) 1		1 (4.2) 3
Splenic infarction		1 (4.2) 1					1 (4.2) 1
Thrombocytosis				1 (4.2) 1			1 (4.2) 1
Cardiac disorders		**1 (4.2) 2**	**1 (4.2) 2**		**1 (4.2) 1**		**2 (8.3) 5**
Acute myocardial infarction					1 (4.2) 1		1 (4.2) 1
Cardiac failure		1 (4.2) 1	1(4.2) 2				1 (4.2) 3
Conduction disorder		1 (4.2) 1					1 (4.2) 1
Gastrointestinal disorders	**4 (16.7) 5**	**2 (8.3) 3**	**1 (4.2) 2**				**7 (29.2) 10**
Abdominal pain			1 (4.2) 1				1 (4.2) 1
Abdominal pain upper	1 (4.2) 1						1 (4.2) 1
Diarrhoea	1 (4.2) 1	1(4.2) 2					2 (8.3) 3
Inguinal hernia		1 (4.2) 1					1 (4.2) 1
Peritoneal disorder	1 (4.2) 1						1 (4.2) 1
Rectal haemorrhage			1 (4.2) 1				1 (4.2) 1
Vomiting	2 (8.3) 2						2 (8.3) 2
General disorders and administration site conditions	**3 (12.5) 3**	**3 (12.5) 3**	**2 (8.3) 2**			**1 (4.2) 1**	**8 (33.3) 9**
Fatigue	1 (4.2) 1	1 (4.2) 1	1 (4.2) 1				3 (12.5) 3
Generalised oedema		1 (4.2) 1					1 (4.2) 1
Non-cardiac chest pain	2 (8.3) 2						2 (8.3) 2
Oedema peripheral		1 (4.2) 1					1 (4.2) 1
Peripheral swelling						1 (4.2) 1	1 (4.2) 1
Pyrexia			1 (4.2) 1				1 (4.2) 1
Immune system disorders	**1 (4.2) 1**						**1 (4.2) 1**
Anaphylactic reaction	1 (4.2) 1						1 (4.2) 1

	Cohort Expansion (N=24)						
SOC/Preferred Term, N (%) E	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Unknown**	**Total**
Infections and infestations	**4 (16.7) 5**	**4 (16.7) 5**	**4 (16.7) 5**		**1 (4.2) 1**		**10 (41.7) 16**
COVID-19			1 (4.2) 1				1 (4.2) 1
Hordeolum		1 (4.2) 1					1 (4.2) 1
Laryngopharyngitis	1 (4.2) 1						1 (4.2) 1
Lower respiratory tract infection	1 (4.2) 1		1 (4.2) 1				2 (8.3) 2
Parotid abscess			1 (4.2) 1				1 (4.2) 1
Parotitis			1 (4.2) 1				1 (4.2) 1
Perineal cellulitis		1 (4.2) 1					1 (4.2) 1
Pneumonia		1 (4.2) 1					1 (4.2) 1
Sepsis					1 (4.2) 1		1 (4.2) 1
Upper respiratory tract infection	2 (8.3) 2						2 (8.3) 2
Urinary tract infection	1 (4.2) 1	1 (4.2) 1					2 (8.3) 2
Wound infection		1 (4.2) 1	1 (4.2) 1				1 (4.2) 2
Injury, poisoning and procedural complications	**1 (4.2) 1**	**2 (8.3) 4**	**2 (8.3) 3**				**4 (16.7) 8**
Eschar			1 (4.2) 1				1 (4.2) 1
Fall	1 (4.2) 1						1 (4.2) 1
Subdural haematoma			1 (4.2) 1				1 (4.2) 1
Subdural haemorrhage			1 (4.2) 1				1 (4.2) 1
Wound		1 (4.2) 2					1 (4.2) 2
Wound complication		1 (4.2) 2					1 (4.2) 2
Investigations	**2 (8.3%) 3**		**1 (4.2) 1**				**3 (12.5) 4**
Alanine aminotransferase increased	1 (4.2) 1						1 (4.2) 1
Blood creatinine increased	1 (4.2) 1						1 (4.2) 1
Blood urea increased	1 (4.2) 1						1 (4.2) 1
Platelet count decreased			1 (4.2) 1				1 (4.2) 1
Metabolism and nutrition disorders	**3 (12.5) 3**	**1 (4.2) 1**					**4 (16.7) 4**
Decreased appetite	2 (8.3) 2						2 (8.3) 2

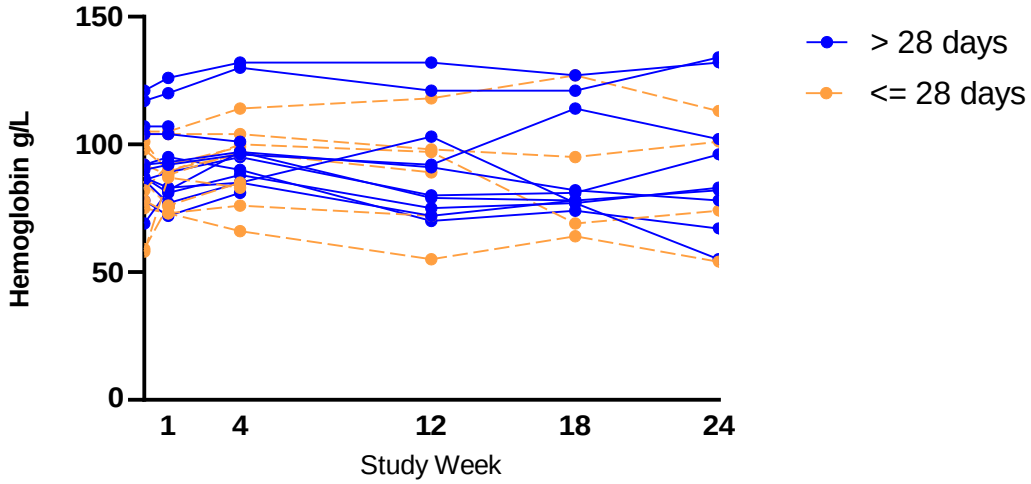
	Cohort Expansion (N=24)						
SOC/Preferred Term, N (%) E	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Unknown**	**Total**
Hyperuricaemia	1 (4.2) 1						1 (4.2) 1
Hypokalaemia		1 (4.2) 1					1 (4.2) 1
Musculoskeletal and connective tissue disorders	**2 (8.3) 4**	**2 (8.3) 2**					**4 (16.7) 6**
Arthralgia	2 (8.3) 2						2 (8.3) 2
Back pain		1 (4.2) 1					1 (4.2) 1
Gouty arthritis		1 (4.2) 1					1 (4.2) 1
Osteoarthritis	1 (4.2) 1						1 (4.2) 1
Pain in extremity	1 (4.2) 1						1 (4.2) 1
Nervous system disorders	**2 (8.3) 2**	**2 (8.3) 4**					**3 (12.5) 6**
Headache	1 (4.2) 1	1 (4.2) 3					1 (4.2) 4
Peripheral sensory neuropathy	1 (4.2) 1						1 (4.2) 1
VIth nerve disorder		1 (4.2) 1					1 (4.2) 1
Psychiatric disorders	**2 (8.3) 2**						**2 (8.3) 2**
Insomnia	2 (8.3) 2						2 (8.3) 2
Renal and urinary disorders	**1 (4.2) 1**	**1 (4.2) 1**					**2 (8.3) 2**
Urinary retention	1 (4.2) 1	1 (4.2) 1					2 (8.3) 2
Reproductive system and breast disorders		**1 (4.2) 1**					**1 (4.2) 1**
Prostatitis		1 (4.2) 1					1 (4.2) 1
Respiratory, thoracic and mediastinal disorders	**1 (4.2) 1**	**1 (4.2) 1**				**1 (4.2) 1**	**3 (12.5) 3**
Epistaxis	1 (4.2) 1						1 (4.2) 1
Respiratory distress		1 (4.2) 1					1 (4.2) 1
Wheezing						1 (4.2) 1	1 (4.2) 1
Skin and subcutaneous tissue disorders	**2 (8.3) 2**	**1 (4.2) 1**	**1 (4.2) 1**				**3 (12.5) 4**
Ecchymosis			1 (4.2) 1				1 (4.2) 1
Purpura		1 (4.2) 1					1 (4.2) 1
Rash	1 (4.2) 1						1 (4.2) 1
Urticaria	1 (4.2) 1						1 (4.2) 1

	Cohort Expansion (N=24)						
SOC/Preferred Term, N (%) E	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Unknown**	**Total**
Vascular disorders		**1 (4.2) 1**					**1 (4.2) 1**
Hypotension		1 (4.2) 1					1 (4.2) 1

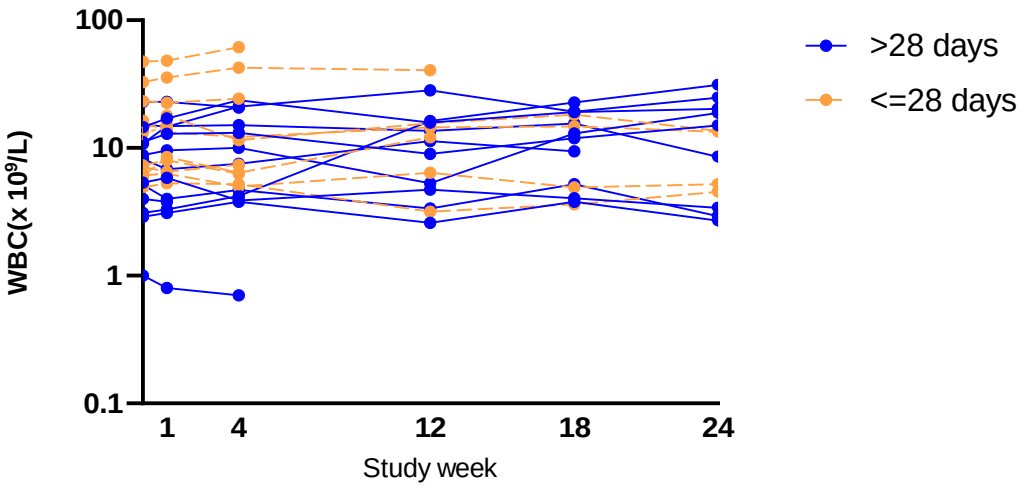
Supplemental Figure 2: Platelet Count (10^9/L) by Patient and Study Week (by interval from prior JAKi therapy)



Supplemental Figure 3: Hemoglobin (g/L) by Patient and Study Week (by interval from prior JAKi therapy)



Supplemental Figure 4: WBC (10^9/L) by Patient and Study Week (by interval from prior JAKi therapy)



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