Abstract 3147.1

A Multicenter, Open-Label, Phase 1 Clinical Trial of AJ1-11095 Administered As Oral Monotherapy in Patients with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post Essential Thrombocythemia Myelofibrosis Who Have Been Failed By a Type I JAK2 Inhibitor

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INTRODUCTION

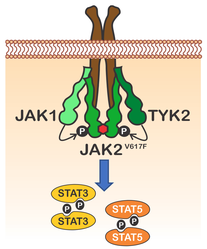
- Myelofibrosis (MF) is a chronic hematologic malignancy with substantial symptom burden, splenomegaly, anemia, and reduced overall survival
- Aberrant JAK-STAT signaling in clonal hematopoietic stem and progenitor cells is a fundamental biologic driver of MF
- The JAK-STAT pathway is the therapeutic target for all four approved Type I JAK2 inhibitors
- While Type I JAK2 inhibitors provide spleen, symptom, and, sometimes anemia improvement, but they do not induce major molecular remission or reliably alter disease course
- Importantly, most patients discontinue Type I JAK2 therapy within 2-3 years of treatment due to lack of clinical response, relapse, disease progression, or adverse events

- **AJ1-11095** is a **first-in-class,** orally bioavailable small molecule **Type II JAK2 inhibitor** designed to overcome a common mechanism of clonal persistence and drug resistance to Type I JAK2 inhibitors

WHAT IS A TYPE II JAK INHIBITOR?

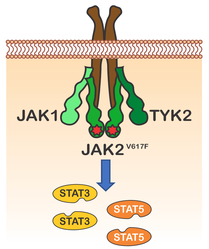
- The JAK2 kinase has two conformations — active "DFG-in" (Type I) and inactive "DFG-out" (Type II)
- **All approved JAK2 inhibitors**, including ruxolitinib, fedratinib, momelotinib and pacritinib, **are Type I inhibitors that bind the *active* conformation only**
- **Type I JAK2 inhibitors' major limitation:** allow JAK2 to form complexes with other JAKs (e.g. JAK2/JAK1, JAK2/TYK2) resulting in "persistent" MPN cells that lose response to Type I therapy
- Previous work showed Type II JAK2 inhibition **overcomes ruxolitinib persistent MPN cells and induces disease modification** in MPN/JAK-mutant leukemia preclinical models

Chronic type I JAK Inhibition



Persistent JAK-STAT Activation

Type II JAK Inhibition



Reversal of Persistent Activation

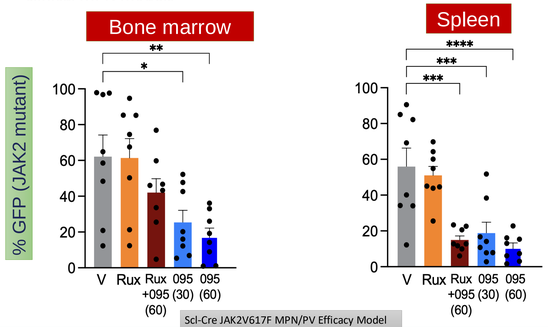
PROTOCOL ELIGIBILITY

Key AJX-101 eligibility criteria:

- Adults ≥18 years with primary MF or post-PV/ ET MF
- Marrow ≤10% blasts, with or without JAK2 mutation
- Intermediate-2 or High-risk disease by Dynamic International Prognostic Scoring System (DIPSS)
- Relapsed/refractory after prior therapy with at least one type I JAK2 inhibitor, either as monotherapy or in combination, *in the judgment of the investigator*
- Spleen volume of ≥450cm^3
- Myelofibrosis Symptom Assessment Form Total Symptom Score (TSS) ≥10, or at least 2 of 7 MFSAF-assessed symptoms with scores ≥3
- Platelet count ≥75 x 10^9 /L
- Neutrophil count ≥1.0 x 10^9 /L
- AST/ALT ≤ 3x upper limit of normal (ULN),
- Estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73m^2
- QTcF ≤ 480ms
- No cytotoxic chemotherapy within 28 days
- Prior JAK2 inhibitor stopped 10 days before C1D1
- Hydroxyurea stopped 5 days before C1D1
- Erythropoiesis-stimulating agents (ESAs) are permitted if on a stable dose for >8 weeks or >5 half-lives

AJ1-11095 BACKGROUND

- AJ1-11095 was designed through computational and structure-based methods to specifically bind the Type II (inactive) conformation of JAK2
- AJ1-11095 is **highly selective for JAK2** compared with other JAK family members (JAK1, JAK3, TYK2)
- Cell line experiments and murine models of MPN show **potent activity of AJ1-11095** both as initial therapy and post ruxolitinib treatment (ruxolitinib persistence model)
- AJ1-11095 ("095") also induces **reduction in the mutant clone** in pre-clinical MPN models

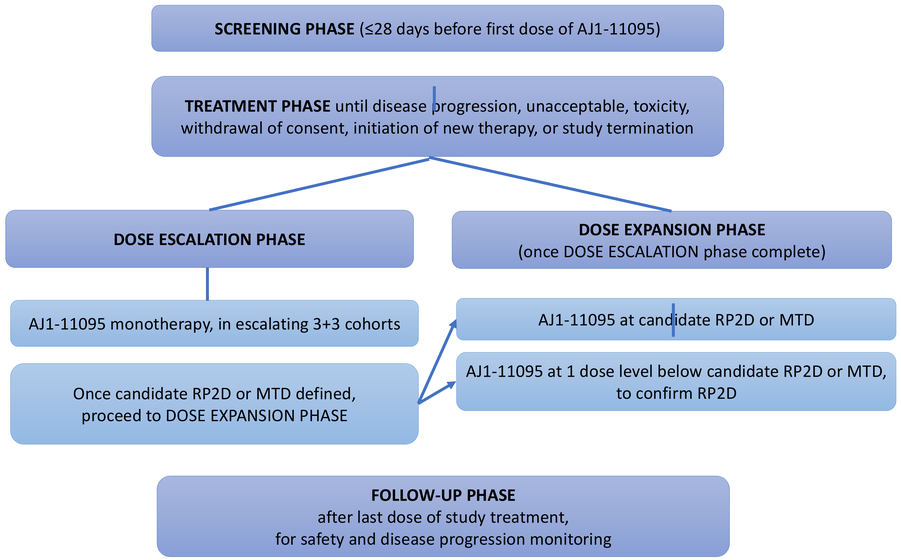


Scl-Cre JAK2V617F MPN/PV Efficacy Model

AJX-101 CLINICAL TRIAL DESIGN

- Phase 1, multicenter, open-label dose escalation and expansion study
- US only initially, then expanding to other regions
- ***First patient enrolled October 2024***

- **Starting dose** of AJ1-11095: **25 mg once daily**
- Dose escalation: conventional 3+3 design
- Subsequent doses determined by a modified Fibonacci sequence and informed by all available safety/tolerability and pharmacokinetics data
- Dose limiting toxicities (DLTs) are defined within the protocol & determined during the first 28-day cycle of treatment
- AE grading: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 5.0



TRIAL ENDPOINTS

Primary objective & endpoint:

- Establish the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of AJ1-11095
- Treatment-emergent adverse events (TEAEs), dose limiting toxicities (DLTs), and changes in clinical laboratory and electrocardiogram (ECG) parameters

Key secondary endpoints:

- Myelofibrosis Symptom Assessment Form Total Symptom Score (TSS) version 4.0 reduction by 50% from baseline to week 24
- Spleen volume reduction (SVR) of ≥35% from baseline to Week 24 measured by imaging
- Characterization of the pharmacokinetics of AJ1-11095
- Changes in blood counts / hematological improvement

Exploratory endpoints:

- Changes in variant allele frequency (VAF) of JAK2 V617F and other clonal markers (somatic mutations)
- Changes in serum levels of pro- inflammatory cytokines influenced by JAK-STAT signaling
- Bone marrow fibrosis grade change

REFERENCES

Koppikar P et al *Nature* 2012; Sep 6;489(7414):155-9

Meyer SC et al *Cancer Cell* 2015; Jul 13;28(1):15-28; 2015

Dunbar AJ et al *Cancer Discovery* 2024 May 1;14(5):737-751

CLINICAL TRIAL REGISTRY

QR code with link to AJX-101 trial at ClinicalTrials.gov

ClinicalTrials.gov ID: NCT06343805