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POIESIS: a phase III study of add-on navtemadlin in JAK inhibitor-naïve myelofibrosis patients with a suboptimal response to ruxolitinib

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ABSTRACT

Most myelofibrosis (MF) patients treated with ruxolitinib fail to achieve optimal response (i.e., spleen volume reduction ≥35% [SVR35] and improvement in total symptom score ≥50% [TSS50], and instead experience suboptimal reductions in spleen volume and constitutional symptoms. Maximizing SVR and TSS is critical for MF patients, as both are associated with improved quality of life (QoL) and overall survival (OS). Navtemadlin is a potent, selective, oral MDM2 inhibitor that restores p53 activity, inducing apoptosis of malignant *TP53* wild-type ($TP53^{WT}$) $CD34^{+}$ MF progenitor cells. In vitro and clinical data demonstrated navtemadlin's synergy with ruxolitinib and disease-modifying potential. POIESIS is a global, randomized, double-blind phase III trial (NCT06479135) evaluating navtemadlin versus placebo as add-on to ruxolitinib in JAK inhibitor-naïve $TP53^{WT}$ MF patients with suboptimal response to ruxolitinib. The study includes a ruxolitinib monotherapy run-in period, followed by randomization of suboptimal responders to add-on navtemadlin or placebo to their stable ruxolitinib dose. Study objectives are to isolate the contribution of add-on navtemadlin by assessing SVR and TSS 24-weeks after randomization from the pre-randomization baseline and to demonstrate that this contribution is clinically meaningful using established SVR and TSS endpoints from the pre-ruxolitinib treatment baseline. Secondary endpoints include progression-free survival, leukemia-free survival, and OS.

Clinical Trial Registration: NCT06479135 (ClinicalTrials.gov); EUCT 2023-504724-25-00 (EUClinicalTrials.EU).

PLAIN LANGUAGE SUMMARY

Myelofibrosis (MF) is a rare blood cancer that affects the bone marrow, causing scarring (fibrosis) and impairing healthy blood cell production. This leads to symptoms, such as fatigue, pain, night-sweats, and an enlarged spleen. Ruxolitinib, a Janus kinase inhibitor (JAKi), is a standard treatment that can reduce spleen size and improve symptoms. However, many MF patients do not respond optimally to ruxolitinib alone, known as a suboptimal response, and continue to experience persistent symptoms and an enlarged spleen. In these cases, adding a new treatment may provide further clinical benefit.

Navtemadlin is an investigational treatment that inhibits MDM2, a protein which is overproduced in MF cancer cells. MDM2 blocks the activity of another protein, p53, a tumor suppressor that normally helps remove abnormal cells. By blocking MDM2, navtemadlin restores the ability of p53 to eliminate MF cancer cells.

The POIESIS study is a global phase III clinical trial testing whether adding navtemadlin to ruxolitinib improves outcomes in MF patients with a suboptimal response to ruxolitinib alone. POIESIS has two treatment periods. During the first period, patients receive ruxolitinib alone for 18–24 weeks. If their response is suboptimal, patients may be eligible to join the second period, where they are randomly assigned to receive either add-on navtemadlin (Arm 1) or placebo (Arm 2) while continuing ruxolitinib. Navtemadlin efficacy will be assessed by measuring the rates of spleen volume reduction (by MRI/CT scan) and total symptom score improvement (using a daily 7-symptom questionnaire), in each arm, 24 weeks after randomization.

ARTICLE HISTORY

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Article highlights

Unmet need in myelofibrosis with a suboptimal response to ruxolitinib

- Myelofibrosis (MF) is a progressive myeloproliferative neoplasm characterized by splenomegaly, debilitating symptoms, bone marrow fibrosis, cytopenias, increased leukemic transformation risk, and shortened survival.
- Standard-of-care ruxolitinib improves spleen volume and symptoms but fails to deliver optimal responses for most patients (i.e., spleen volume reduction ≥35% [SVR35], and total symptom score improvement ≥50% [TSS50]).
- The magnitude of spleen and symptom improvement correlate with overall survival (OS).
- Ruxolitinib has limited disease-modifying activity, and most patients eventually require additional therapy.
- No approved add-on therapies exist for MF patients with suboptimal response to ruxolitinib, highlighting a significant unmet need.

Navtemadlin: a first-in-class oral MDM2 inhibitor

- MF is characterized by overexpression of mouse double minute 2 (MDM2) in malignant $CD34^+$ progenitor cells, enabling evasion of p53-mediated apoptosis.
- Navtemadlin is a potent, selective, oral MDM2 inhibitor that restores p53 tumor suppressor function, inducing apoptosis of $TP53^{WT}$ $CD34^+$ MF progenitor cells.

Rationale for for navtemadlin add-on to ruxolitinib

- Navtemadlin's mechanism is distinct from and complementary to ruxolitinib, as demonstrated in preclinical studies using patient-derived MF cells.
  - Clinical studies have demonstrated navtemadlin's efficacy, safety, and disease-modifying potential.
  - In the phase III BOREAS trial, navtemadlin monotherapy achieved Week-24 SVR35 (15% vs 5%) and TSS50 (24% vs 12%) versus best available therapy (BAT) in JAKi-relapsed/refractory MF.
  - In a phase Ib/II study (KRT-232-109; NCT04485260), navtemadlin add-on to ruxolitinib achieved Week-24 SVR35 and TSS50 in 32% of $TP53^{WT}$ MF patients with suboptimal response.
  - Both studies demonstrated reductions in circulating CD34+ MF cells and driver mutation variant allele frequencies (VAFs) by Week 24.
  - In BOREAS, navtemadlin-driven SVR correlated with reductions in circulating $CD34^+$ MF cells ($p = 0.001$) and VAF ($p < 0.001$).
  - Acute myeloid leukemia (AML) transformations occurred less frequently with navtemadlin than BAT (1.6% vs 3.3%).

POIESIS: a novel phase III trial design

- POIESIS (NCT06479135, EUCT 2023-504724-25-00) is a global, randomized, double-blind, placebo-controlled phase III study evaluating navtemadlin add-on therapy in JAK inhibitor-naïve $TP53^{WT}$ Primary or Secondary MF patients with suboptimal response to ruxolitinib.
- The study includes an initial ruxolitinib run-in followed by a randomized add-on period, reflecting a real-world treatment approach, in which add-on therapy is introduced only for patients with suboptimal response.
- Eligibility requires a stable ruxolitinib dose (≥5 mg BID) for ≥8 weeks and a suboptimal response (SVR >0% but <35% and TSS improvement >0% but <50%) after >18-weeks of ruxolitinib.
- Patients are randomized 2:1 to add-on navtemadlin (240 mg QD, Days 1–7 of a 28-day cycle) or placebo.
- Crossover is not permitted to preserve progression-free survival (PFS), leukemia-free survival (LFS), and OS endpoints.
- Approximately 600 patients are enrolling across ~254 sites in >23 countries.

POIESIS objectives and endpoints

- To isolate navtemadlin's contribution by comparing SVR and TSS improvement at Week 24 from the pre-randomization baseline.
- To confirm clinically meaningful benefit using established SVR and TSS endpoints relative to the pre-ruxolitinib baseline.

Conclusion

- POIESIS may establish navtemadlin as the first effective add-on therapy for JAKi-naïve MF patients with suboptimal response to ruxolitinib, addressing a major unmet need and potentially redefining the MF treatment paradigm.

1. Trial overview

POIESIS (NCT06479135, EUCT 2023-504724-25-00) is a global, registrational, randomized, double-blind, placebo-controlled phase III trial designed to evaluate the efficacy and safety of navtemadlin, a selective mouse double minute 2 (MDM2) inhibitor, as add-on therapy to ruxolitinib in JAK inhibitor-naïve patients with *TP53* wild-type ($TP53^{WT}$) primary or secondary myelofibrosis (MF) who have a suboptimal response to ruxolitinib. The study design includes two treatment periods: an initial ruxolitinib monotherapy run-in phase (≥18 to <25 weeks) followed by a randomized add-on period.

During the run-in period, ruxolitinib may be titrated to a stable, tolerable dose (≥5 mg twice daily). To be eligible for randomization, patients must have received a stable dose of ruxolitinib for ≥8 consecutive weeks and met criteria for suboptimal response, defined as SVR >0% but <35% and TSS improvement >0% but <50%. Eligible patients are randomized 2:1 to receive navtemadlin (240 mg QD, Days 1–7 of a 28-day cycle; Arm 1) or placebo (Arm 2), both as add-on to their stable dose of ruxolitinib.

The study aims to isolate the clinical contribution of navtemadlin by comparing SVR (by central review MRI/CT scan) and TSS (by the Myelofibrosis Symptom Assessment Form version 4.0 [MFSAF v4.0]) responses from pre-randomization baselines and confirm clinically meaningful benefit using established SVR and TSS endpoints from pre-ruxolitinib baselines, all assessed 24 weeks post-randomization. Crossover is not permitted to preserve the integrity of survival endpoints: progression-free survival (PFS), which includes leukemia-free survival (LFS), and overall survival (OS).

The trial name, POIESIS (**P**53 activation to **O**pt**I**miz**E** response**S** in myelofibros**IS**) derives from the Greek words ποιειν (poiein), which means "to bring into being," and αιματο-ποιησις (hemato-poiesis), the process that produces blood cells in the body.

2. Background and rationale

2.1. Myelofibrosis

Myelofibrosis (MF) is a chronic, progressive malignancy of the bone marrow (BM), with an estimated prevalence of 4–6 per 100,000 in the US [1]. MF is the most aggressive myeloproliferative neoplasm (MPN), characterized by clonal proliferation of malignant hematopoietic stem cells, megakaryocytic proliferation with atypia, overproduction of inflammatory cytokines and progressive BM fibrosis resulting in ineffective and extramedullary hematopoiesis [2]. Prominent clinical manifestations of MF include marked splenomegaly, debilitating constitutional symptoms (pruritus, fatigue, weight loss, cachexia, arthralgia, night sweats, abdominal pain/fullness, and early satiety) [2], and progressive anemia [3]. Constitutive activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway is a hallmark of MF, commonly driven by somatic mutations in one of the MPN "driver" genes (*JAK2*, *CALR*, and *MPL*) [4]. High molecular risk

mutations in epigenetic regulators (e.g., *ASXL1*, *EZH2*, *IDH1/2*) and splicing factors (e.g., *SRSF2*, *U2AF1*) are also strongly implicated in MF pathophysiology and poor prognosis [4–6]. Advanced MF is associated with poor quality of life (QoL) and a high risk of transformation to blast phase MPN (blast count ≥20% in the peripheral blood [PB] or BM) [5,6]. The median overall survival (OS) in MF is markedly shortened (4–7 years in primary MF [PMF]) [7], even more so in high-risk MF (median OS approximately 2 years [8]). Although allogeneic stem cell transplantation (allo-SCT) offers curative potential for intermediate-2 to high-risk MF, high transplant-related morbidity and mortality preclude its use for most patients [9].

2.2. Unmet medical need in MF patients with a suboptimal response to ruxolitinib

Ruxolitinib was the first JAK1/2 inhibitor that received regulatory approval in 2011 as a treatment for intermediate- or high-risk MF, including PMF, post-polycythemia vera (PV) MF, and post-essential thrombocythemia (ET) MF. Subsequently, three other JAK inhibitors (JAKis), fedratinib, pacritinib, and momelotinib, were approved for MF in the US in 2019, 2022, and 2023, respectively [10]. These JAKis target the aberrant JAK-STAT signaling pathway and deliver a reduction in spleen volume and symptom burden [2,11], with momelotinib also improving anemia [12]. However, responses to JAKis are suboptimal in a significant proportion of patients, and their clinical efficacy may be lost over time. Furthermore, JAKis are associated with high rates of treatment discontinuation: more than one-third of patients discontinue ruxolitinib, with 35% of cases resulting from lack or loss of spleen response [13]. Discontinuation rates reached 50% at 3 years and 75% at 5 years for MF patients randomized to ruxolitinib in the COMFORT-I trial [14,15]. After ruxolitinib discontinuation, patient outcomes are dismal, with a median OS of 11–13 months [16–18].

As previously stated, the majority of MF patients treated with standard-of-care ruxolitinib [19,20] fail to achieve an optimal response, defined as realizing both SVR35 *and* TSS50. In frontline phase III trials (COMFORT-I, SIMPLIFY-1, and MANIFEST-2), SVR35 was achieved in 29–42% and TSS50 in 42–46% of patients at week 24, yet <20% achieved both [21–23]. Similarly, in the phase III COMFORT-II study, <30% of patients achieved an optimal response at week 48 [24].

Optimizing spleen and symptom responses is of paramount importance given their strong association with QoL [25–27] and OS [18,28–32]. In COMFORT-I, TSS was found to be inversely correlated with QoL ($p < 0.001$) [27], with constitutional symptoms now integrated into MF prognostic scoring systems [2]. Verstovsek et al. reported significantly longer OS in ruxolitinib-treated MF patients who achieved SVR ≥50% versus SVR <25% ($p < 0.0001$) [18]. Accordingly, in a pooled analysis of COMFORT I and II studies, SVR ≥10% to <25% was associated with twofold higher OS hazard ratio (HR) compared to SVR ≥50% [28]. A meta-analysis including COMFORT-I, SIMPLIFY-1, and PERSIST-2 clinical trials and five retrospective studies confirmed that JAK inhibitor-treated MF patients who achieved a particular relative SVR threshold (>50%, >35%, >25%) had 55% lower mortality risk (HR 0.45; $p < 0.001$) compared to patients on the same JAKi who did not reach these endpoints [30]. In RUXOREL-MF, a real-world study in ruxolitinib-treated patients, a palpable spleen length reduction ≤30% at 3 and 6 months from the baseline was associated with worse OS ($p = 0.0009$) [29].

Similar to other JAKis, ruxolitinib can reduce spleen volume and improve symptoms, but it has limited ability to deliver disease-modifying effects and change the underlying natural history of the disease (prevent clonal evolution and progression) [33,34]. As a result, the majority of MF patients who initiate ruxolitinib treatment will ultimately require an additional therapeutic intervention. The absence of any proven add-on therapy in the context of suboptimal response to ruxolitinib represents an area of high unmet medical need. In this setting, the optimal intervention is an add-on treatment that delivers both clinical and disease-modifying effects to improve long-term patient outcomes.

2.3. Navtemadlin's mechanism of action

As the key negative regulator of p53, MDM2 modulates the function of p53 by inhibiting its downstream transcriptional activity, promoting its transport out of the nucleus, and ubiquitinating the protein for proteasomal degradation [35]. While *TP53* mutations are infrequent in MPNs (<5%), p53 activity is often suppressed by constitutive JAK2-mediated signaling in $CD34^+$ MF cells, leading to MDM2 overexpression and the quiescence of p53. This represents the central mechanism by which MF cells evade normal p53 tumor suppressor detection and apoptosis, enabling malignant cell survival.

Navtemadlin is a potent, selective, and orally available MDM2 inhibitor that restores normal p53 tumor-suppressor function in *TP53* wild-type ($TP53^{WT}$) malignancies [36]. P53-dependent apoptosis of malignant cells occurs via upregulation of select pro-apoptotic B-cell lymphoma 2 (BCL-2) family proteins (e.g., BAX, PUMA, NOXA), and equivalent downregulation and suppression of pro-survival proteins (e.g., Bcl-2, Bcl-X_L, Mcl-1) [37,38]. *In vitro* testing of navtemadlin in $TP53^{WT}$ tumor cell lines demonstrated its ability to markedly induce dose-dependent activation of p53, leading to inhibition of cell proliferation. Data from xenograft testing in murine $TP53^{WT}$ models showed that navtemadlin induced robust p21-mediated cell-cycle arrest and apoptosis [39]. A first-in-human phase I study confirmed navtemadlin's dose-dependent pharmacokinetics/pharmacodynamics, safety, and antitumor activity in $TP53^{WT}$ malignancies [40]. Recent trials further demonstrated navtemadlin's ability to significantly reduce malignant $CD34^+$ MF progenitor cells [41–44].

2.4. Efficacy of navtemadlin monotherapy in JAK-inhibitor refractory/relapsed MF

In a phase II dose escalation study (NCT03662126; KRT-232-101 Part A), conducted in $TP53^{WT}$ patients with MF who were relapsed/refractory (R/R) to JAKis, navtemadlin 240 mg orally, once daily on Days 1–7 of 28-day cycles, was established as the recommended phase II dose (RP2D) and schedule [45].

In the global, randomized phase III BOREAS study (NCT03662126; KRT-232-101 Part B), navtemadlin monotherapy was compared with best available therapy (BAT) in *TP53*^{WT} MF patients R/R to JAKis [38]. At week 24, navtemadlin achieved SVR35 (primary endpoint) and TSS50 (key secondary endpoint) in 15% (18/123) and 24% (30/123) of patients, respectively, with response rates threefold (SVR) and twofold (TSS) higher than BAT (5% and 12%, respectively) [46].

2.5. In vitro evidence of navtemadlin-ruxolitinib synergy in MF cells

Navtemadlin's mechanism (p53-mediated apoptosis of malignant CD34$^+$ MF cells) is distinct from, and complementary to, ruxolitinib's inhibition of the JAK-STAT signaling pathway. In vitro studies showed that navtemadlin and ruxolitinib synergistically enhanced apoptosis in MF patient-derived CD34$^+$ progenitor cells by inhibition of p21-mediated cell-cycle arrest [47].

2.6. Clinical evidence of navtemadlin-ruxolitinib synergy in patients with MF

In the Ib/II dose-escalation study (NCT04485260; KRT-232-109) of navtemadlin add-on to ruxolitinib in *TP53*^{WT} patients with MF who had a suboptimal response to ruxolitinib, the RP2D, and schedule of navtemadlin was determined to be 240 mg once daily (Day 1–7/28-day cycle) [44]. In this study, and in contrast to POIESIS, suboptimal response was defined as lack of spleen response or disease progression per International Working Group-Myeloproliferative Neoplasms Research and Treatment [IWG-MRT] criteria [48]. Enrolled patients had received ruxolitinib for ≥18 weeks and were on a stable dose for ≥8 weeks. The baseline characteristics of patients in the KRT-232-109 study were similar to those enrolled in the BOREAS study; at study entry, the median duration of prior ruxolitinib exposure was 21.6 months, approximately 50% of patients had anemia grade ≥2, and the median spleen volume and TSS were >2,000 cm^3 and ≥15, respectively [44].

Consistent with the in vitro results, clinical data evidenced the robust efficacy and synergy of navtemadlin add-on to ruxolitinib, with 32% (6/19) of patients achieving SVR35 (primary endpoint) and TSS50 (key secondary endpoint) at week 24 in the KRT-232-109 study (Figure 1; intention-to-treat [ITT] population; data cut-off May 2023) [44]. Notably, patients had received ruxolitinib for a very long period of time prior to study entry, with most on doses ≥15 mg twice daily, and yet they were still unable to achieve an optimal response [44]. Ruxolitinib dose increases were not permitted, confirming that the observed clinical responses were attributable to navtemadlin [44].

2.7. Disease-modifying activity of navtemadlin

Studies of navtemadlin monotherapy [41–43] and navtemadlin add-on to ruxolitinib [44] have demonstrated on-target biological activity and provided supporting evidence for potential disease modification. In myeloproliferative neoplasms, disease modification requires that a therapeutic intervention not only alters the underlying biological mechanisms driving the disease, such as aberrant stem cell function or clonal architecture, but also translates into a demonstrable clinical benefit including improved survival or prevention of disease progression [49]. While current agents have yet to meet this stringent definition, including those tested in combination with JAK inhibitors [50], indicators such as reductions in circulating CD34$^+$ MF cells, driver mutation variant allele frequency (VAF), proinflammatory cytokine levels, and improvements in bone marrow fibrosis are commonly employed as surrogates for disease-modifying activity. Here, navtemadlin therapy resulted in substantial reductions in circulating CD34$^+$ MF cells, driver mutation variant allele frequency (VAF), and improvement of bone marrow fibrosis.

In both the phase II and phase III BOREAS studies [41,43], reductions in circulating CD34$^+$ MF progenitor cells are significantly correlated with SVR ($p = 0.0048$ and $p = 0.001$, respectively). In the BOREAS study, the median circulating CD34$^+$ MF cell count reductions were −62% at Week 12 and −82% at Week 24 with navtemadlin (versus −52% and −42% with BAT) [43]. Among patients with >50% CD34$^+$ MF cell count reduction at Week 24, 40% of navtemadlin-treated patients achieved SVR35 versus 20% with BAT [43]. Reductions in driver mutation VAF ($p < 0.001$) and selected serum-measurable inflammatory cytokines ($p < 0.001$ for all) at Week 24 also correlated with SVR [43]. Similarly, in the Ib/II navtemadlin add-on study (KRT-232-109), median circulating CD34$^+$ progenitor cell counts decreased by −85% and −95% at 12 and 24 weeks, respectively (Figure 2) [44].

These findings corroborate that navtemadlin-induced apoptosis of CD34$^+$ MF progenitor cells translates into improved clinical outcomes in monotherapy and ruxolitinib combination treatment settings. Optimizing SVR and TSS is essential due to their established relationship with QoL [25,26] and OS [18,28–31].

Furthermore, in the BOREAS study, the incidence of transformation to acute myeloid leukemia (AML) on the navtemadlin-treated arm was 1.6%, while that of the BAT arm was 3.3% [46] in an advanced relapsed/refractory MF population; supporting the hypothesis of disease modification with navtemadlin and its potential for reduction in risk of AML progression (MPN Blast Phase) relative to existing therapies. Collectively, this evidence supports MDM2 inhibition as a promising and disease-modifying novel therapeutic approach for the treatment of MF across the R/R and suboptimal response settings.

2.8. Navtemadlin safety and tolerability

In the phase Ib/II KRT-232–109 trial in *TP53*^{WT} MF patients with suboptimal response to ruxolitinib [44], and the phase III BOREAS study [46], navtemadlin, administered at the RP2D, demonstrated a manageable safety profile, particularly upon adoption of prophylactic measures for gastrointestinal side effects. The most common treatment-emergent adverse events, consistent with on-target MDM2 inhibition, were gastrointestinal (diarrhea, nausea, vomiting), and hematologic (thrombocytopenia, anemia, neutropenia).

2.9. POIESIS study rationale

The complementary mechanisms of navtemadlin and ruxolitinib, their demonstrated preclinical synergy, the encouraging clinical efficacy, and acceptable safety of navtemadlin in monotherapy and add-on studies, and navtemadlin's disease-modifying

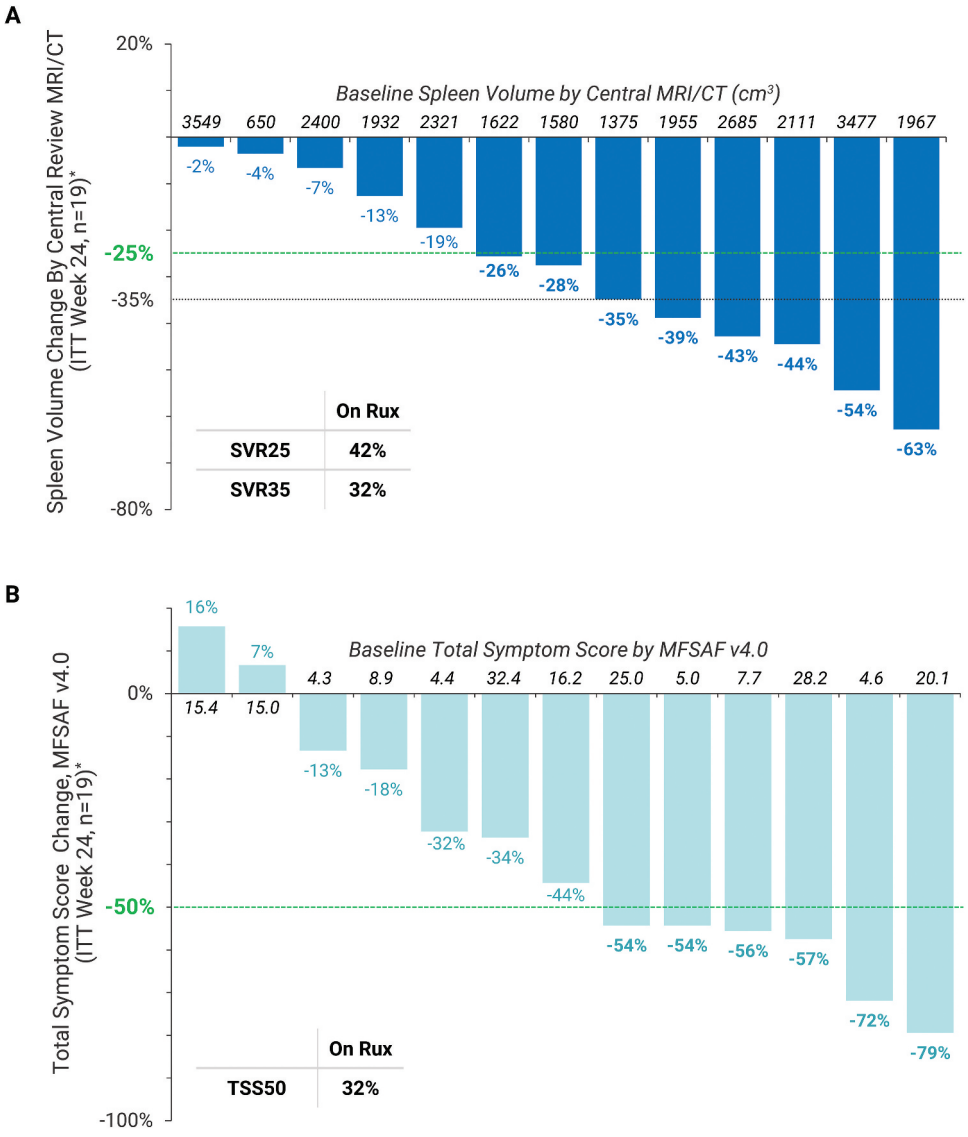


Figure 1. Week 24 spleen volume reduction (by central MRI/CT) and total symptom score (by MFSAF v4.0). Baseline spleen volume MRI/CT scans and TSS assessments were taken while subjects were on a stable dose of ruxolitinib for ≥8 weeks (ie, no ruxolitinib wash-out). No dose increases of ruxolitinib above the stable baseline dose occurred during the 24-week assessment period. Both SVR35 and TSS50 were 32% at Week 24. Median time on ruxolitinib monotherapy was 21.6 months (data cut-off May 2023; ref. [44]). *Six patients discontinued prior to Week 24 assessment.

Abbreviations: CT, Computed tomography; ITT, Intention to treat; MFSAF v4.0, Myelofibrosis Symptom Assessment Form version 4.0; MRI, Magnetic resonance imaging; Rux, Ruxolitinib; SVR25, Spleen volume reduction ≥25%; SVR35, Spleen volume reduction ≥35%; TSS50, Total symptom score ≥50%.

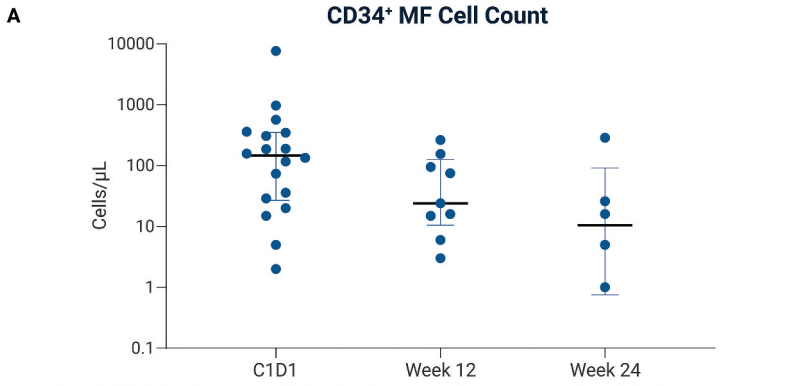
potential, together support the scientific and clinical rationale for the POIESIS study (NCT06479135; KRT-232-115) [35].

3. The POIESIS phase III trial design

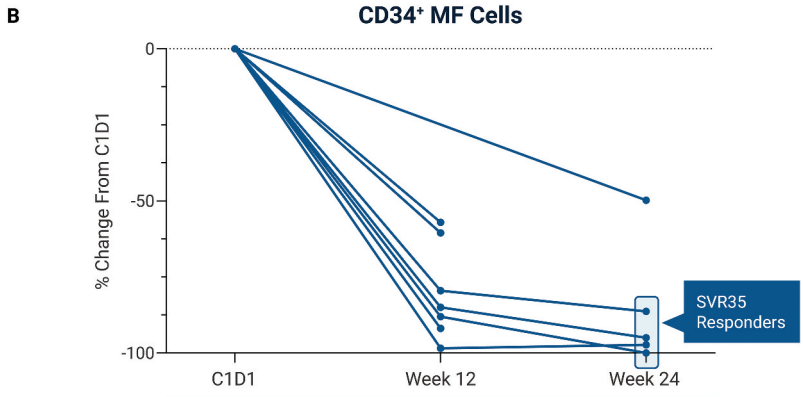
POIESIS (NCT06479135, EUCT 2023-504724-25-00) is a global, randomized, double-blind, placebo-controlled III clinical study designed to evaluate the efficacy and safety of navtemadlin as an add-on to ruxolitinib for the treatment of JAK inhibitor-naïve *TP53*^{WT} patients with PMF, post-PV MF, or post-ET MF with a suboptimal response to ruxolitinib [51]. POIESIS has a unique and innovative trial design that mimics the real-world MF treatment approach by reserving navtemadlin add-on therapy for those patients who demonstrate a suboptimal response to ruxolitinib and are therefore in need of an additional clinical intervention.

3.1. Eligibility criteria

Eligibility for enrollment to the ruxolitinib monotherapy run-in period (Table 1) includes: adults aged ≥18 years with a confirmed diagnosis of PMF, post-PV MF, or post-ET MF (per 2022 WHO criteria [1]), classified as intermediate- or high-risk MF according to the International Prognostic Scoring System (IPSS) [8], and with an Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤2. Additional requirements include a spleen volume ≥450 cm^3; TSS ≥10 by MFSAF v4.0 at baseline; and adequate hematologic, hepatic, and renal



	C1D1	Week 12	Week 24
Median (cells)	146	24	10
Mean (cells)	621	73	56
N	18	9	6*



	C1D1	Week 12	Week 24
Median (%)		-85	-95
Mean (%)		-80	-86
N		7	5

Figure 2. Reduction in circulating CD34$^+$ MF progenitor cell counts in study KRT-232-109 (data cut-off April 2023 [44]). *One patient with a cell count of 0 at Week 24 not shown on this figure.

Abbreviations: C1D1, Cycle 1, Day 1; MF, Myelofibrosis; SVR35, Spleen volume reduction ≥35%.

organ function. Importantly, participants must be JAK inhibitor-naïve.

Key exclusion criteria for the ruxolitinib run-in period include prior exposure to inhibitors of JAK, MDM2, Bcl-xL, BET, PI3K, PIM kinase, or XPO1, prior p53-directed therapies; previous allo-SCT or eligibility for immediate allo-SCT (i.e., patients with an available donor who are deemed to be clinically appropriate to proceed to allo-SCT without delay); and PB or BM blast count ≥10%. Patients achieving optimal spleen or symptom response (i.e., SVR35 or TSS50), or those who are refractory (i.e., with disease progression), will be discontinued from the study after the run-in period.

Eligibility for the randomized period (Table 1) includes confirmed *TP53*^{WT} status (by central testing) and a suboptimal response to ruxolitinib monotherapy, defined as SVR >0% but <35% *and* TSS improvement >0% but <50%, assessed following 18–25 weeks of ruxolitinib treatment. Participants must be receiving a stable ruxolitinib dose (≥5 mg twice daily) for ≥8 continuous weeks prior to assessment for randomization to add-on navtemadlin or placebo.

Key exclusion criteria for randomization include a white blood cell count that increases twofold or more during ruxolitinib therapy (baseline prior to the run-in period versus pre-randomization) and exceeds 50×10^9/L at pre-randomization, and PB or BM blast counts ≥10%.

3.2. Study design

POIESIS features an innovative, pragmatic, and practice-aligned design (Figure 3), structured around two treatment periods: a ruxolitinib monotherapy run-in period (N = 600), followed by a randomized, placebo-controlled phase (N = 180) for JAKi-naïve MF patients with suboptimal response to standard-of-care ruxolitinib treatment.

During the ruxolitinib run-in period, eligible patients receive ruxolitinib for ≥18 but <25 weeks. A stable ruxolitinib dose (≥5 mg twice daily; investigator determined) must be maintained for ≥8 continuous weeks prior to randomization. A stable dose is defined as one that has not required dose modification or interruption during the 8-week lead-in.

Table 1. Key eligibility criteria.

Inclusion criteria
Ruxolitinib monotherapy run-in period
• JAK inhibitor-naïve patients
• Age ≥18 years
• Confirmed diagnosis of PMF, post-PV MF, or post-ET MF (WHO criteria [52])
• Intermediate-1, intermediate-2, or high-risk MF (by IPSS [8])
• Spleen volume ≥450 cm^3 by MRI or CT scan (central review)
• MF symptoms as defined by baseline TSS ≥10 (calculated 7-day average by the MFSAF v4.0 [53])
• ECOG PS ≤2
• Adequate hematologic function (platelet count ≥100x10^9/L, white blood cell count ≤50x10^9/L, and ANC count ≥1.5x10^9/L)
• Adequate hepatic and renal organ function
Randomized period
• PMF, post-PV MF, or post-ET MF
• *TP53*^{WT} assessed by central testing
• ECOG PS ≤2
• Ruxolitinib monotherapy treatment for ≥18 weeks but <25 weeks on a stable dose of ruxolitinib (≥5 mg BID) for ≥8 continuous weeks prior to add-on treatment with navtemadlin
• Suboptimal response to ruxolitinib, defined as:
• SVR >0% but <35% by MRI/CT scan (central review) *and* TSS reduction >0% but <50% (measured by the MFSAF v4.0) from the start of the ruxolitinib run-in period baseline to the end of the run-in period
• Adequate hematologic function (platelet count ≥ 100x10^9/L, ANC count ≥1.5x10^9/L)
• Adequate hepatic and renal organ function
Exclusion criteria
Ruxolitinib monotherapy run-in period
• Prior treatment with any JAK inhibitor
• Prior therapy with MDM2, BcL-xL, BET, PI3K, PIM, or XPO1 inhibitors; prior p53-directed therapy
• Prior splenectomy
• Splenic irradiation within 3 months prior to the first dose of ruxolitinib monotherapy
• Active or chronic bleeding within 28 days prior to the first dose of ruxolitinib monotherapy
• Prior allogeneic SCT or eligibility for allogeneic SCT
• Peripheral blood or bone marrow blast count ≥10% at any time within 28 days prior to the first dose of ruxolitinib monotherapy
• Grade 2 or higher QTc prolongation (480 milliseconds per NCI-CTCAE, version 5.0)
• Active serious infection or uncontrolled intercurrent illness
Randomized period
• Active treatment with inhibitors of MDM2, Bcl-xL, BET, PI3K, PIM, and XPO1 or p53-directed therapy
• Splenic irradiation within 3 months prior to the first dose of study treatment in the randomized period
• Eligibility for allogeneic SCT
• White blood cell count that meets both of the following criteria: – Increases by two-fold or more during treatment with ruxolitinib monotherapy (compared to baseline prior to the run-in period versus pre-randomization) and – Exceeds 50×10^9/L at pre-randomization
• Blast count ≥10% in the peripheral blood or bone marrow at any time within 28 days prior to the first dose of study treatment in the randomized period

Abbreviations: ANC: Absolute neutrophil count; BCL-xL: B-cell lymphoma-extra-large; BET: Bromodomain and extra-terminal; BID: twice daily; CT: Computed tomography; ECOG PS: Eastern Cooperative Oncology Group performance status; IPSS: International Prognostic Scoring System; JAK: Janus kinase; MDM2: Murine double minute 2; MF: Myelofibrosis; MFSAF v4.0: Myelofibrosis Symptom Assessment Form version 4.0; MRI: Magnetic resonance imaging; NCI-CTCAE v5.0: National Cancer Institute-Common Terminology Criteria for Adverse Events, version 5.0; PI3K: Phosphoinositide 3-kinase; PIM: Proviral Integration site for Moloney leukemia virus; PMF: Primary MF; Post-ET MF: Post-essential thrombocythemia MF; Post-PV MF: Post-polycythemia vera MF; QTc: Corrected QT interval; SCT: Stem cell transplantation; SVR: Spleen volume reduction; *TP53*^{WT}: Wild-type tumor protein p53 gene; TSS: Total symptom score; XPO1: Exportin 1; WHO: World Health Organization.

After completing the ruxolitinib run-in period, patients with confirmed *TP53*^{WT} status and a protocol-defined suboptimal response will be randomized 2:1, in a double-blind manner, to receive add-on navtemadlin (Arm 1, n = 120) or add-on placebo (Arm 2, n = 60). Patients in Arm 1 will receive navtemadlin at 240 mg once daily (Day 1–7/28-day cycle) [44] added on to their ongoing stable dose of ruxolitinib (≥5 mg twice daily). Patients in Arm 2 will receive matching placebo added on to their ongoing stable dose of ruxolitinib, as per Arm 1. Escalation of ruxolitinib dose above the pre-randomization stable dose is not permitted before the primary efficacy assessment. Stratification factors include ruxolitinib dose at randomization (<20 mg BID vs ≥20 mg BID), and magnitude of SVR (<20% vs ≥20%) and TSS (<30% vs ≥30%) following the ruxolitinib run-in period.

Crossover between arms is not permitted to preserve the integrity of survival endpoints including PFS (including leukemia-free survival), and OS, which are important secondary endpoints.

3.3. Study objectives and endpoints

The POIESIS study has two primary objectives (Table 2). First, to isolate the clinical contribution of add-on navtemadlin in patients with suboptimal response to ruxolitinib, by evaluating SVR (by central review MRI/CT scan) and symptom burden (by MFSAF v4.0) 24 weeks after randomization relative to the pre-randomization baseline. Second, to assess whether this contribution is clinically meaningful by evaluating the proportion of patients achieving established SVR and TSS reduction, 24 weeks after randomization relative to their pre-ruxolitinib treatment baseline.

Key secondary endpoints (Table 3) are PFS (including LFS) and OS in Arm 1 versus Arm 2, duration of spleen responses,

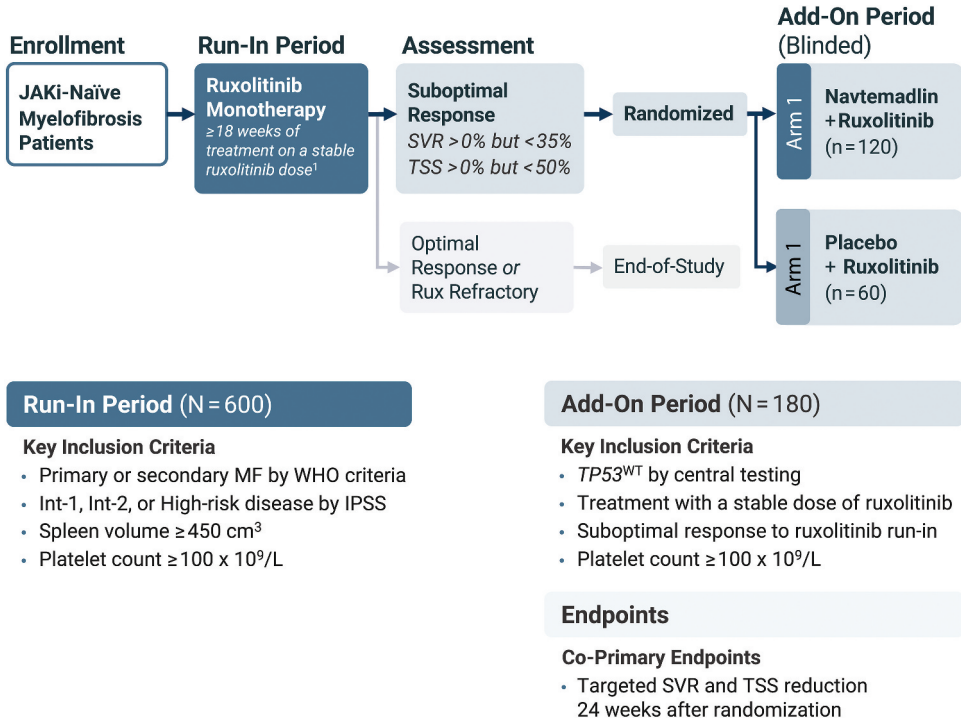


Figure 3. POIESIS study schema.

Note: Navtemadlin dosed at 240 mg QD (Days 1–7/28-day cycle). Target enrollment from 254 sites across 23 countries.

[1]Stable ruxolitinib is ≥5 mg BID that does not require treatment hold or dose adjustment during the 8-weeks prior to add-on navtemadlin or placebo.

Abbreviations: BID, twice daily; Int, Intermediate; IPSS, International Prognostic Scoring System; JAKi, Janus kinase inhibitor; Rux, Ruxolitinib; SVR, Spleen volume reduction; TSS, Total symptom score; WHO, World Health Organization; WT, Wild-type.

Table 2. Study aims.

• Adequately isolate the contribution of add-on navtemadlin in the setting of continuous ruxolitinib by assessing SVR and TSS at 24 weeks after randomization from the pre-randomization baseline
• Demonstrate that this contribution is clinically meaningful by using established SVR (by MRI/CT, central review) and TSS (by MFSAF v4.0) endpoints at 24weeks after randomization from the pre-ruxolitinib treatment baseline

Abbreviations: CT: Computed tomography; MFSAF v4.0: Myelofibrosis Symptom Assessment Form version 4.0; MRI: Magnetic resonance imaging; SVR: Spleen volume reduction; TSS: Total symptom score.

and safety of navtemadlin versus placebo when added to ruxolitinib. Exploratory endpoints (Table 3) include other quality of life measures and changes in potential markers of disease modification, such as circulating $CD34^+$ cell counts, driver and high molecular risk (HMR) mutations, blood inflammatory markers, and changes in bone marrow fibrosis (baseline to 24 weeks after randomization, and every 24 weeks thereafter).

3.4. Assessments

Spleen volume will be assessed by using MRI or CT imaging, with all scans reviewed by an independent blinded central imaging vendor. Symptom burden will be measured using the MFSAF v.4.0, comprising 7 core symptoms (fatigue, bone pain, pruritus, night sweats, abdominal discomfort, pain under the ribs on the left side, and early satiety) [2]. Patients will complete daily symptom diaries, and weekly TSS will be calculated as the average of daily scores over a 7-day period. This same method was used in all navtemadlin studies discussed herein, except for study KRT-232-101 Part A where the modified MFSAF v2.0 was used [45]. All biomarker evaluations and assessments will be independently conducted by central testing.

3.5. Interventions

During the run-in period, ruxolitinib dose reductions may be considered at the investigator's discretion to manage treatment-emergent thrombocytopenia and anemia, known effects of ruxolitinib [19].

In the randomized phase of POIESIS, patients receiving navtemadlin will also receive anti-emetic prophylaxis with ondansetron 8 mg orally twice daily; administered 30 min before and 8 hr after each navtemadlin dose on Days 1–7 of each 28-day cycle. Ondansetron may be continued on navtemadlin non-treatment days at the investigator's discretion. Additionally, patients will receive anti-diarrheal prophylaxis with loperamide 2 mg orally twice daily on navtemadlin treatment days for at least the first two cycles. Patients randomized to placebo will receive matching placebo prophylactic medications.

During the randomized phase, per-protocol dose modifications of navtemadlin/placebo and/or ruxolitinib are based on the nature and severity of the adverse event (hematologic or non-hematologic), the patient's stable ruxolitinib dose at the time of the event, and the frequency of prior toxicity occurrences. Escalation or re-scalation of ruxolitinib dose above the pre-randomization stable dose is not permitted during the randomized period.

Table 3. Study endpoints.

Co-primary endpoints	● Proportion of patients who achieve targeted SVR by MRI/CT (central review), in each arm, at 24 weeks post-randomization from the pre-randomization baseline ● Proportion of patients who achieve targeted TSS (by MFSAF v4.0), in each arm, at 24 weeks post-randomization from the pre-randomization baseline ● Proportion of patients who achieve established SVR threshold by MRI/CT (central review), in each arm, at 24 weeks post-randomization from the pre-ruxolitinib baseline ● Proportion of patients who achieve established TSS threshold (by MFSAF v4.0), in each arm, at 24 weeks post-randomization from the pre-ruxolitinib baseline
Key secondary endpoints	● Progression-free survival (including leukemia-free survival) in each arm ● Overall survival in each arm ● Duration of spleen response in each arm ● Spleen response rate (by MRI/CT) at any time in the randomized period in each arm ● Spleen size reduction as measured by palpation in each arm ● Safety and tolerability of navtemadlin versus placebo as add-on to ruxolitinib
Exploratory endpoints	● Time to achieve spleen response and symptom response in each arm ● Quality of life in each arm ● Clinical efficacy of navtemadlin versus placebo as add-on to ruxolitinib as correlated with selected biomarkers, including the following: – Circulating $CD34^+$ MF cell counts in the peripheral blood – High molecular risk mutations – Blood inflammatory markers ● Changes in MPN driver gene VAF in each arm (central testing) ● Changes in the bone marrow in each arm (central review)

Abbreviations: CT: Computed tomography; MFSAF v4.0: Myelofibrosis Symptom Assessment Form version 4.0; MRI: Magnetic resonance imaging; SVR: Spleen volume reduction; TSS: Total symptom score.

Study treatment will continue until disease progression per modified IWG-MRT criteria [50] (≥25% spleen volume enlargement compared with baseline, or leukemic transformation), unacceptable toxicity, death, or withdrawal of consent. Patients who discontinue treatment due to disease progression will be monitored long-term for survival and subsequent anticancer therapy every 12 weeks until the end of the study.

3.6. Study size and timeline

Approximately 600 JAK inhibitor-naïve MF patients are expected to be enrolled to achieve the target 180 patients randomized into the add-on treatment period. The sample size was selected to ensure adequate statistical power based on data from a prior study of navtemadlin add-on to ruxolitinib [44]. The study is projected to conclude approximately 24 months after the last patient is randomized. At that timepoint, patients who remain on study treatment may be considered for eligibility to enroll in a rollover study.

3.7. Study enrollment sites

POIESIS is being conducted in approximately 254 cancer centers across at least 23 countries, including the United States, the United Kingdom, Australia, Belgium, Croatia, France, Georgia, Germany, Greece, Italy, Romania, Serbia, and Spain. Enrollment began in late 2024, and the study is actively recruiting patients at the time of this publication. A complete list of study sites is available at ClinicalTrials.gov (NCT06479135), EUClinicaTrials.EU (EUCT 2023-504724-25-00) and https://poiesis-trial.com/.

3.8. Statistical analysis

Descriptive statistics will summarize data from the ruxolitinib run-in period. Efficacy analyses will be evaluated on the ITT population. For the co-primary and secondary endpoints, two-arm response rates will be tested using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factors, and the difference between the two arms will be displayed with 95% confidence intervals. Analysis of time-to-event endpoints, such as OS, will be provided based on Kaplan-Meier estimates. All randomized patients who receive ≥1 dose of navtemadlin or placebo will be included in the safety analyses.

4. Conclusion

Previous registrational phase III trials have shown that fewer than 30% of JAK inhibitor-naïve MF patients achieve an optimal response (i.e., SVR35 and TSS50) with ruxolitinib monotherapy, highlighting an urgent unmet need for improved therapeutic strategies.

POIESIS is a global, registrational, randomized phase III study designed to evaluate the efficacy and safety of navtemadlin as an add-on to ruxolitinib for the treatment of JAK inhibitor-naïve *TP53*^{WT} MF patients who have a suboptimal response to ruxolitinib. The POIESIS trial is strongly supported by data evidencing preclinical synergy of the combination with complementary mechanisms of action, robust clinical

results from navtemadlin monotherapy and add-on studies, and disease-modifying potential demonstrated by prominent surrogate biomarker changes.

The POIESIS trial features an innovative and unique design that includes an initial ruxolitinib run-in period followed by a randomized add-on phase, reflecting a real-world treatment approach, in which add-on therapy is introduced for patients with a suboptimal response to standard-of-care treatment. The study objectives will determine the clinical benefit of add-on navtemadlin in the setting of continuous ruxolitinib use and assess if this contribution is clinically meaningful in patients with a suboptimal response.

Taken together, POIESIS represents a promising opportunity to advance treatment for MF patients and evaluate the clinical benefit of a novel, mechanism-based, disease-modifying strategy in a population with a persistent unmet need.

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Ethical declaration

Signed informed consent is required by patients prior to study initiation. The POIESIS study protocol is approved by the Institutional Ethics Review Board of each participating study site. The study is being performed in accordance with the ethical principles of the Declaration of Helsinki and conducted in line with the International Conference for Harmonization Guidelines for GCP and region-specific laws and regulations. This manuscript has been developed in adherence with SPIRIT guidelines.

Data sharing statement

As this is a Trial-in-Progress article, study data, the protocol, the statistical analysis plan and any other study-related documents will not be shared at this time.

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