Clinical Trial Protocol

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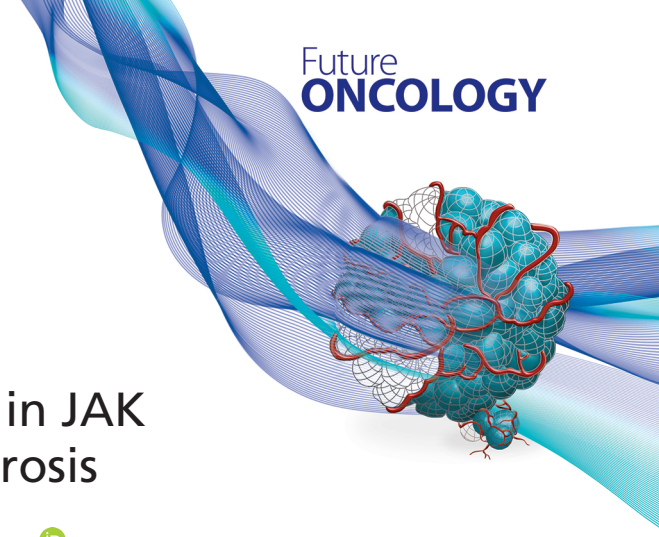

Phase III MANIFEST-2: pelabresib + ruxolitinib vs placebo + ruxolitinib in JAK inhibitor treatment-naive myelofibrosis

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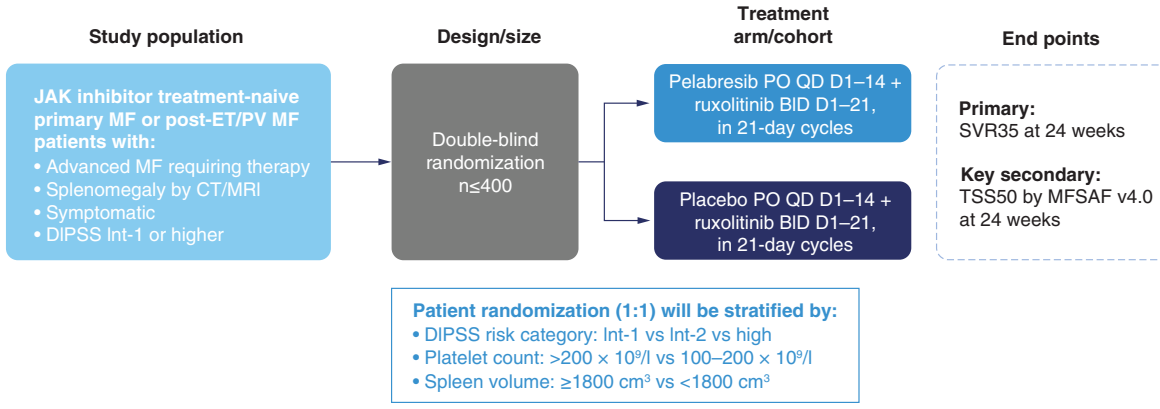
Myelofibrosis (MF) is a clonal myeloproliferative neoplasm, typically associated with disease-related symptoms, splenomegaly, cytopenias and bone marrow fibrosis. Patients experience a significant symptom burden and a reduced life expectancy. Patients with MF receive ruxolitinib as the current standard of care, but the depth and durability of responses and the percentage of patients achieving clinical outcome measures are limited; thus, a significant unmet medical need exists. Pelabresib is an investigational small-molecule bromodomain and extraterminal domain inhibitor currently in clinical development for MF. The aim of this article is to describe the design of the ongoing, global, phase III, double-blind, placebo-controlled MANIFEST-2 study evaluating the efficacy and safety of pelabresib and ruxolitinib versus placebo and ruxolitinib in patients with JAKi treatment-naive MF.

Clinical Trial Registration: NCT04603495 (ClinicalTrials.gov)

Future Medicine

Plain language summary: Myelofibrosis (MF) is a rare type of blood cancer that interferes with the process of blood cell production by the bone marrow. In patients with MF, the bone marrow becomes overactive, leading to scarring and subsequently a lack of healthy blood cells being produced. The main symptoms of MF include anemia, fatigue, weakness and pain or discomfort in the abdomen. MF is associated with a shortened life expectancy. The current go-to treatment for MF is ruxolitinib. However, ruxolitinib has shown limited efficacy in improving clinical symptoms long term; so, new safe and effective treatments are needed. Pelabresib is a novel drug currently in clinical development for treating MF. The aim of this article is to describe the design of the ongoing, global phase III MANIFEST-2 study. MANIFEST-2 is evaluating the efficacy and safety of pelabresib and ruxolitinib versus placebo and ruxolitinib in patients with MF.

Graphical abstract:



Tweetable abstract: Read up on the ongoing MANIFEST-2 trial evaluating #pelabresib and ruxolitinib in JAKi treatment-naive patients with #myelofibrosis in this recently published #openaccess article

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Keywords: CPI-0610 • JAKi treatment-naive • MANIFEST-2 • myelofibrosis • pelabresib • ruxolitinib

Myelofibrosis (MF) is a clonal myeloproliferative neoplasm (MPN) that includes primary MF as well as MF that develops after a diagnosis of polycythemia vera or essential thrombocythemia [1,2]. The main hallmarks of overt MF are splenomegaly, disease-related symptoms, cytopenias and bone marrow fibrosis. As such, MF is associated with fatigue, abdominal pain, pruritus, night sweats, weight loss, bone pain, thrombohemorrhagic complications and progressive cytopenias often requiring red blood cell (RBC) transfusions [1,2]. The progressive bone marrow fibrosis associated with MF impairs normal hematopoiesis in the bone marrow, contributing to extramedullary hematopoiesis [1,2].

Approximately 9 of 10 cases of MF are considered intermediate to high risk, categories that are associated with reduced survival (reported median survival for intermediate-1 risk, 6.5–7.8 years; intermediate-2 risk, 2.9–3.6 years; high risk, 1.3–1.8 years) [3,4]. The significant symptom burden, splenomegaly, poor quality of life and reduced survival experienced by these patients are all strongly linked with progressive bone marrow fibrosis [3,5].

Allogeneic stem cell transplantation (ASCT) is currently the only potentially curative approach for MF and can be considered in patients <70 years and with intermediate-2 or high-risk disease [6]. However, few patients are eligible due to the associated morbidity and mortality in this patient population [1], and, as such, ASCT is used in <20% of patients [4]. The JAK inhibitors (JAKis) ruxolitinib [7], fedratinib [8] and pacritinib [9] have been US FDA approved for the treatment of adult patients with intermediate-2 or high-risk MF. All three agents have demonstrated splenic responses and symptom improvement in phase III clinical studies [1,10–13]. While pacritinib is approved for intermediate- or high-risk MF patients with platelets $<50 \times 10^9$/l [9], ruxolitinib and fedratinib are the current standard of care according to the National Comprehensive Cancer Network guidelines in higher-risk patients with platelets $\geq 50 \times 10^9$/l and ineligible for ASCT [14]. In both COMFORT-I and -II studies [1,10], ruxolitinib performed significantly better than placebo and best available therapy, respectively, in terms of ≥35% spleen volume reduction from baseline (SVR35; 41.9 vs 0.7%; $p < 0.001$ at week 24 in COMFORT-I; 28 vs 0%,

$p < 0.001$ at week 48 in COMFORT-II) [1,10]. Additionally, in COMFORT-I, the reduction in total symptom score of ≥50% from baseline (TSS50) at week 24 was significantly higher for ruxolitinib versus placebo (45.9 vs 5.3%, respectively [$p < 0.001$]) [1]. In the JAKARTA study, both fedratinib 400 mg and 500 mg once daily (QD) performed significantly better than placebo in terms of SVR35 (36 and 40%, respectively, vs 1%; $p < 0.001$) and TSS50 (36 and 34%, respectively, vs 7%, $p < 0.001$) at week 24 [12].

Despite now being an established therapy for MF, treatment with ruxolitinib is subject to a number of limitations, such as failure to obtain a significant reduction in splenomegaly or symptom response, and the development or persistence of clinically significant cytopenias [15–17]. Furthermore, there is typically a gradual loss of response to ruxolitinib over time and a lack of evidence for a long-term effect on disease biology [18]. Median time to treatment discontinuation with ruxolitinib has been found to be less than 1 year in a real-world setting [19]. In turn, discontinuation of ruxolitinib can result in accelerated splenomegaly, ruxolitinib discontinuation syndrome and poor outcomes [20,21]. Additionally, patients who do not derive adequate benefit from ruxolitinib have a poor prognosis and/or overall survival (OS) [19,22,23].

As such, there is an unmet need for treatment options for patients with MF that improve upon the spleen and symptom responses seen with JAKi monotherapy, reduce bone marrow fibrosis associated with MF and ameliorate the cytopenias associated with MF and with ruxolitinib.

MANIFEST-2 trial

Here we describe the rationale and design for the phase III MANIFEST-2 (ClinicalTrials.gov, NCT04603495) trial, which will evaluate the efficacy and safety of pelabresib (CPI-0610) and ruxolitinib versus placebo and ruxolitinib in patients with JAKi treatment-naive MF. This study is sponsored by Constellation Pharmaceuticals a MorphoSys Company.

Background & rationale

BET proteins regulate transcription of a set of genes that integrate a diverse array of oncogenic abnormal signals. BET inhibition has the potential to modify multiple critical components of MF pathobiology, including megakaryocyte differentiation and proliferation [24–27]. Bone marrow fibrosis in MF develops as a result of aberrant megakaryopoiesis and expression of proinflammatory cytokines [25–27]. These two processes, heavily influenced by BET-mediated gene regulation, lead to myeloproliferation, cytopenias and reticulin deposition and result in disease-related morbidity and mortality [25,27,28]. More recently, elevated proinflammatory cytokines present in MF have been linked to NF-κB [26]. Through its effect on the NF-κB signaling pathway, inhibition of BET proteins can reduce proinflammatory cytokine expression [26,29]. In preclinical murine models of MF, BET inhibition resulted in reduced proinflammatory cytokine levels, spleen weight and bone marrow fibrosis [26].

Pelabresib is an oral, small-molecule investigational BET inhibitor (BETi) that is designed to modify the expression of genes involved in NF-κB signaling in patients with MF (Figure 1) [25,27,28,30]. Pelabresib has demonstrated the potential to change the natural disease course of MF through several mechanisms, including reprogramming of NF-κB-controlled gene expression, such as the proinflammatory gene *IL-8* [31]. Pelabresib modulates megakaryopoiesis and key NF-κB signaling nodes in MF, resulting in reduction in proinflammatory cytokines known to play a role in bone marrow fibrosis. Preclinical studies suggest that a combination of a BETi and JAKi can result in synergistic reduction of splenomegaly, bone marrow fibrosis and proinflammatory cytokines [26]. These findings support the potential complementary activity of pelabresib and a JAKi for MF treatment [26,29].

Pelabresib is currently being investigated in the phase II MANIFEST study (NCT02158858) as a monotherapy in patients with MF who are refractory/intolerant or ineligible for JAKi therapy (arm 1), or in combination with ruxolitinib in patients who have suboptimal or lost response to ruxolitinib (arm 2), or in combination with ruxolitinib in JAKi treatment-naive patients with MF (arm 3).

Data from arm 3 of MANIFEST, which include JAKi treatment-naive patients with MF, show robust responses in spleen volumes and symptoms after 24 weeks of treatment with pelabresib and ruxolitinib [32,33]. The combination of pelabresib and ruxolitinib led to 68% (57/84) of patients achieving SVR35 at week 24 [32], with a median spleen volume reduction of -50%. Most patients reported symptomatic improvement on the Myelofibrosis Symptom Assessment Form (MFSAF), with 56% (46/82) achieving TSS50 at week 24, and a median change in TSS of -59% [32]. Pelabresib in combination with ruxolitinib was generally well tolerated; observed events of thrombocytopenia were mostly of low grade, manageable and reversible [32,33]. Data from arms 1 and 2 of the MANIFEST phase II study indicate that pelabresib treatment can lead to improvements in transfusion dependence

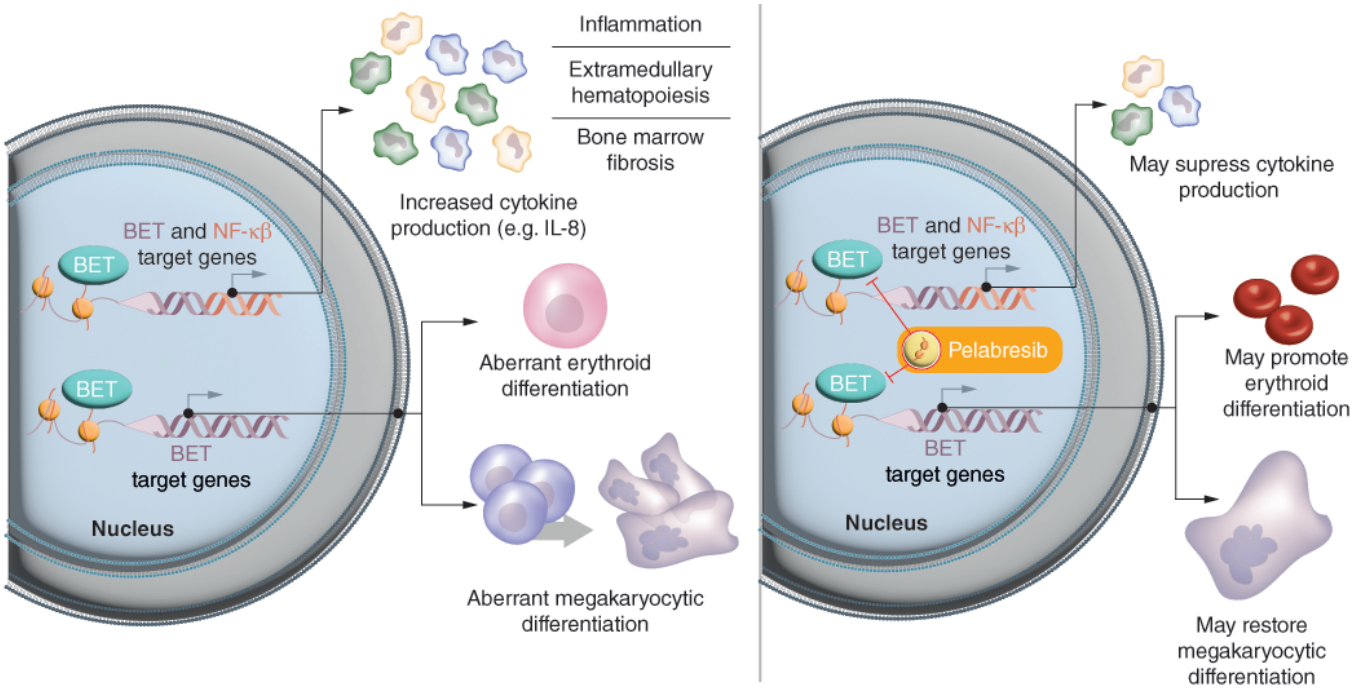

Figure 1. Pelabresib proposed mechanism of action in myelofibrosis.

and hemoglobin levels [34,35]. Additionally, an exploratory analysis across all three arms of MANIFEST has also shown that treatment with pelabresib has positive effects on megakaryocyte differentiation and maturation, and erythropoiesis [32]. Based on these encouraging results, the MANIFEST-2 study was initiated.

Data from the three arms of the MANIFEST study in patients with MF indicate that pelabresib impacts cytokine expression and bone marrow function [34,36]. Overall, the reduction of several plasma cytokines involved in the NF-κB pathway and proinflammatory signaling during treatment with pelabresib monotherapy or pelabresib and ruxolitinib was rapid and durable [34,36]. A total of 23, 25 and 31% of patients in arm 1 (pelabresib monotherapy in patients refractory or intolerant or ineligible for JAKi therapy), arm 2 (pelabresib in combination with ruxolitinib for MF patients with suboptimal/lost response to ruxolitinib) and arm 3 (pelabresib and ruxolitinib in JAKi treatment-naive patients), respectively, had achieved ≥1 grade improvement in bone marrow fibrosis at week 24 by central pathology review [32,34].

Study design

MANIFEST-2 (NCT04603495) is a global phase III, multicenter, randomized, double-blind, placebo-controlled study of pelabresib and ruxolitinib versus placebo and ruxolitinib in JAKi treatment-naive patients with MF (Figure 2). Following a screening period of ≤28 days, eligible patients are randomized in a 1:1 ratio using a centralized interactive voice response system/interactive web response system to receive either pelabresib and ruxolitinib or placebo and ruxolitinib. Stratification is based on the Dynamic International Prognostic Scoring System (DIPSS) risk category (intermediate-1 vs intermediate-2 vs high), platelet count (>200 × 10^9/l vs 100–200 × 10^9/l) and spleen volume (≥1800 cm^3 vs <1800 cm^3).

Pelabresib or matched placebo are administered QD for 14 consecutive days, followed by a 7-day break (21-day cycle). The starting dose for pelabresib/placebo is 125 mg QD for all patients, with subsequent dose increases permitted as per protocol criteria. Ruxolitinib is administered twice daily (BID) for all 21 days of each cycle at either 10 or 15 mg BID, depending on patient baseline platelet counts; dose increases are permitted as per protocol criteria. Patients are treated until disease progression or discontinuation/withdrawal of treatment, and are followed up for progression-free survival (PFS) and OS. Patients enrolled in the placebo and ruxolitinib group, who experience disease progression after 24 weeks of treatment, may be crossed over to the pelabresib and ruxolitinib group. Disease

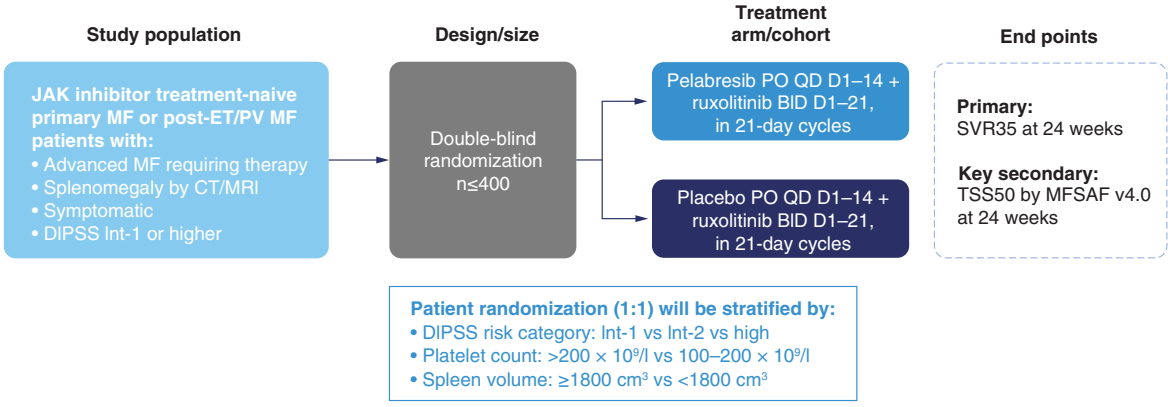

Figure 2. MANIFEST-2 study design.
BID: Twice daily; CT: Computerized tomography; D: Day; DIPSS: Dynamic International Prognostic Scoring System; ET: Essential thrombocythemia; Int-1: Intermediate-1; Int-2: Intermediate-2; MF: Myelofibrosis; MFSAF: Myelofibrosis Symptom Assessment Form; PO: By mouth; PV: Polycythemia vera; QD: Once daily; SVR35: ≥35% spleen volume reduction from baseline; TSS50: Reduction in total symptom score of ≥50% from baseline.
Reproduced with permission from [37].

Table 1. Study population, objectives and end points for MANIFEST-2.

Study population	
Key inclusion criteria	**Key exclusion criteria**
• Age ≥18 years • Confirmed diagnosis of MF (primary MF, post-polycythemia vera MF or post-essential thrombocythemia MF) • Adequate hematologic, renal and hepatic function • Have ≥2 symptoms with an average score ≥3 or an average total score of ≥10 over the 7-day period prior to randomization using the MFSAF v4.0 • Prognostic risk-factor score of intermediate-1 or higher per DIPSS • Spleen volume of ≥450 cm^3 • ECOG performance status of ≤2	• Splenectomy or splenic irradiation within 6 months prior to anticipated C1D1 • Chronic or active conditions and/or concomitant medication use that would prohibit participation in trial • Prior treatment with any JAKi or BETi for the treatment of a myeloproliferative neoplasm • Candidate for, and willing to undergo allogeneic HSCT
Study end points	
Primary	**Key secondary**
Splenic response, defined as a ≥35% reduction from baseline in SVR (SVR35), as measured by MRI or CT, at week 24	TSS response, defined as a ≥50% decrease from baseline in TSS (TSS50), as measured by the MFSAF v4.0, at week 24
Objective	
To determine the efficacy and safety of pelabresib and ruxolitinib compared with placebo and ruxolitinib	

BETi: BET inhibitor; C1D1: Cycle 1 day 1; CT: Computerized tomography; DIPSS: Dynamic International Prognostic Scoring System; ECOG: Eastern Cooperative Oncology Group; HSCT: Hematopoietic stem cell transplant; JAKi: JAK inhibitor; MF: Myelofibrosis; MFSAF: Myelofibrosis Symptom Assessment Form; SVR: Spleen volume reduction; TSS: Tumor symptom score.

progression for crossover eligibility is defined as progressive splenomegaly with enlargement of spleen volume of ≥25% compared with baseline.

Eligibility criteria

The study population consists of patients ≥18 years of age with a confirmed diagnosis of MF (primary MF, post-polycythemia vera MF or post-essential thrombocythemia MF) with adequate hematologic, renal and hepatic function and a prognostic risk score of intermediate-1 or higher per DIPSS. Patients must also have at least two symptoms with an average score ≥3 or an average total score of ≥10 over the 7-day period prior to randomization using the MFSAF v4.0, spleen volume of ≥450 cm^3 and Eastern Cooperative Oncology Group performance status ≤2. Patients will be excluded if they have had splenic irradiation in the previous 6 months or a splenectomy, chronic or active conditions, and/or concomitant medication use that would interfere with study treatment or prior treatment with any JAKi or BETi for treatment of a MPN. A summary of key study eligibility criteria is shown in Table 1.

Planned sample size & study period

Planned enrollment is for up to approximately 400 patients in total (up to 200 in the pelabresib and ruxolitinib group, and up to 200 in the placebo and ruxolitinib group). Study enrollment sites are currently located in the USA, Australia, Canada and Europe (Austria, Belgium, France, Hungary, Italy, The Netherlands, Poland, Spain and UK).

Study procedures

Patient demographics are documented during screening, and a complete medical history is collected, including current/past medical conditions and concomitant medications. The patient's disease status is evaluated by measurement of peripheral blood counts, history/documentation of transfusion requirements, MF-associated symptoms, spleen size by palpation and by MRI and/or computed tomography (CT), and grading of bone marrow fibrosis, as assessed by bone marrow biopsy. Patients are required to complete the MFSAF assessment daily, the Patient Global Impression Scale assessment electronically weekly after the start of study treatment and the EQ-5D assessment electronically weekly during screening and treatment. All patients are assessed for toxicity by the investigator per US National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0. For all treatment-emergent adverse events (TEAEs), the investigator will determine if these can be attributed to either pelabresib or, in the case of Germany, the study drugs. Blood samples are collected for the determination of pelabresib and ruxolitinib concentrations in plasma, and biomarker assessments are completed for each patient at certain timepoints.

Outcome measures/end points

The primary efficacy end point of the current study is splenic response at week 24 versus baseline, defined as SVR35 measured by MRI or CT (Table 1). The key secondary end point is TSS50 at week 24 versus baseline, measured by the MFSAF v4.0. Other secondary end points include percentage change in TSS at week 24 versus baseline, improvement in bone marrow fibrosis by $\geq$1 grade at week 24 versus baseline, SVR35 and TSS50 response at week 48 versus baseline, rate of RBC transfusions over the first 24 weeks of treatment, conversion from RBC transfusion dependence to independence, category change of Patient Global Impression of Change at week 24 versus baseline, survival (PFS and OS), percentage of patients with transformation to acute myeloid leukemia, adverse events of all grades and serious adverse events, population pharmacokinetics assessment and descriptive assessment of ruxolitinib plasma concentrations in the presence or absence of ruxolitinib.

Statistics

Analysis methods

The primary analysis will take place after all randomized patients have either completed their week 24 visit or been prematurely discontinued. Until the primary analysis takes place, patients, investigators and the sponsor will remain blinded to patient allocation to study arms, except for those patients who were enrolled into the crossover portion of the study at or after week 24 and therefore had to be unblinded.

The response rates for SVR35 and TSS50 will be tested sequentially using the Cochran–Mantel–Haenszel test stratified by baseline DIPSS (intermediate-1 vs intermediate-2 vs high), platelet count (100–200 $\times$ 10^9/l vs $>$200 $\times$ 10^9/l) and spleen volume ($<$1800 cm^3 vs $\geq$1800 cm^3). As a result of sequential testing, no multiplicity adjustment will be made.

Sample size

Approximately 400 patients will be enrolled in the study (up to 200 in each treatment group) such that sequential treating of the primary (SVR35) and key secondary (TSS50) end points are adequately powered for 2-group continuity corrected χ^2 text.

Conclusion

The current standard of care for symptomatic patients with newly diagnosed MF is treatment with a JAKi. While pacritinib is approved for intermediate- or high-risk MF patients with platelets $<$50 $\times$ 10^9/l [9], ruxolitinib and fedratinib are the recommended JAKis in higher-risk patients with platelets $\geq$50 $\times$ 10^9/l and ineligible for ASCT [14]. However, JAKis offer limited benefits, and a substantial proportion of patients will discontinue JAKi treatment due to progressive disease and TEAEs, such as anemia and thrombocytopenia [16,17,38]. Patients discontinuing JAKi generally have poor prognosis [19,22,23]. A potential reason for this is that MF is a heterogenous

and genetically and biologically complex disease, and JAKi monotherapy affects only some of its pathogenic drivers. As such, there is currently an unmet need for new and improved treatment options targeting different pathogenic pathways in MF. Synergistic therapeutic agents such as a rational combination strategy are needed, including agents with a novel mechanism of action with potential for disease-modifying effects leading to overall improvement in the prognosis of MF. Preclinical studies suggest that inhibition of both BET and JAK pathways using a rational combination strategy can result in reduction of splenomegaly, bone marrow fibrosis and mutant allele burden [28], and improve the outcomes currently achieved with JAKi monotherapy.

In arm 3 of the phase II MANIFEST study, the combination of pelabresib and ruxolitinib was well tolerated and demonstrated clinically meaningful durable improvements in spleen volume and symptoms in a JAKi treatment-naive patient population with MF [32,33]. While previous pivotal studies on JAKi monotherapy showed SVR35 response rates of 29–42% at week 24 [1,10–12] in arm 3 of MANIFEST, 68% of patients achieved SVR35 at week 24 [32]. Analysis of long-term follow-up data from COMFORT-I and -II revealed that a reduction in palpable spleen size was associated with prolonged survival, as such promoting spleen reduction as a meaningful clinical trial end point [39]. Furthermore, while real-world ruxolitinib discontinuation is frequent (1-, 2- and 3-year rates of 49%, 71% and 86% [n = 51], respectively) [17,23], as of the most recent data cutoff only 25% (20/81) of patients in MANIFEST arm 3 discontinued pelabresib combined with ruxolitinib within 1 year (three patients ongoing but not yet reached 1 year) despite adverse baseline characteristics.

As in the phase II MANIFEST trial, a lower starting dose of ruxolitinib in cycle 1 (5 mg BID below the recommended dose in the local approved product labeling) will be used in order to enhance tolerability during the first cycle. The ruxolitinib dose will be increased at cycle 2 day 1 (i.e., after 3 weeks) to the target dose levels per approved product labeling as long as prespecified criteria are met. This approach is aligned with clinical practice [40].

The phase III MANIFEST-2 trial is designed to evaluate the efficacy and safety of pelabresib with ruxolitinib in JAKi treatment-naive patients with MF. It is the first study of its kind assessing combination therapy as first-line treatment for patients with MF without prior JAKi exposure. It aims to investigate whether pelabresib in combination with ruxolitinib will result in improved efficacy outcomes compared with ruxolitinib versus placebo [1]. Additionally, assessing rational combination therapy as a first-line treatment option has the potential to lead to a paradigm shift for treatment of MF, favoring upfront combination therapy, without prior JAKi monotherapy failure. MANIFEST-2 was opened for enrollment in November 2020 and, as of the time of this publication, is currently recruiting patients. For additional information on the MANIFEST-2 study please visit the NCT website [41].

Executive summary

Introduction

- Myelofibrosis (MF) is a clonal myeloproliferative neoplasm, typically associated with constitutional symptoms, splenomegaly, anemia and bone marrow fibrosis.
- Patients with MF experience a significant symptom burden and a reduced life expectancy.
- The current standard-of-care for symptomatic patients with newly diagnosed MF is treatment with a JAK inhibitor (JAKi).
- However, JAKis offer limited benefits, and a substantial proportion of patients will discontinue JAKi treatment due to progressive disease and treatment-emergent adverse events, such as anemia and thrombocytopenia. Patients discontinuing JAKis generally have poor prognosis.
- As such, there is currently an unmet need for new and improved treatment options targeting different pathogenic pathways in MF.

Background & rationale

- Pelabresib is an investigational small-molecule bromodomain and extraterminal domain inhibitor currently in clinical development for MF.
- Pelabresib is currently being investigated in the phase II MANIFEST study (NCT02158858) as monotherapy in patients with MF who are refractory/intolerant or ineligible for JAKi therapy (arm 1), or in combination with ruxolitinib in patients who have suboptimal or lost response to ruxolitinib (arm 2), or in combination with ruxolitinib in JAKi treatment-naive patients with MF (arm 3).
- Data from arm 3 of MANIFEST show robust responses in spleen volumes and symptoms after 24 weeks of treatment with pelabresib and ruxolitinib. Additionally, an exploratory analysis across all three arms of MANIFEST has shown that treatment with pelabresib has positive effects on megakaryocyte differentiation and maturation, and erythropoiesis. Based on these and other encouraging results, the MANIFEST-2 study was initiated.

MANIFEST-2 study design & planned sample size

- The phase III MANIFEST-2 trial (NCT04603495) is designed to evaluate the efficacy and safety of pelabresib with ruxolitinib in JAKi treatment-naive patients with MF.

- Approximately 400 patients will be enrolled in MANIFEST-2 (up to 200 each in the pelabresib and ruxolitinib and placebo and ruxolitinib treatment groups).

Conclusion

- MANIFEST-2 is the first study of its kind assessing combination therapy as first-line treatment for patients with MF without prior JAKi exposure. It aims to investigate whether pelabresib in combination with ruxolitinib will result in improved efficacy outcomes compared with ruxolitinib versus placebo.
- MANIFEST-2 was opened for enrollment in November 2020 and, as of the time of this publication, is currently recruiting patients.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: https://www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0484

Author contributions

Each co-author listed participated sufficiently in the work to take responsibility for the content and that all those who qualify are listed. Authorship credit is based on (a) substantial contributions to the conception or design of the work or the acquisition, analysis or interpretation of data for the work; and (b) drafting the work or revising it critically for important intellectual content; and (c) final approval of the version to be published; and (d) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have met conditions (a), (b), (c) and (d).

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, for investigations, informed consent has been obtained from the participants involved.

Data sharing statement

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

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