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Protocol for Study M16-191

Myelofibrosis: Phase 3 Study of Navitoclax Plus Ruxolitinib Versus Ruxolitinib

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FULL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Navitoclax in Combination with Ruxolitinib Versus Ruxolitinib in Subjects with Myelofibrosis (TRANSFORM-1)

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1 SYNOPSIS

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Navitoclax in Combination with Ruxolitinib Versus Ruxolitinib in Subjects with Myelofibrosis (TRANSFORM-1)	
Background and Rationale:	Current therapies, other than hematopoietic stem cell transplantation (HSCT), are not able to control all the clinical manifestations of myelofibrosis (MF). Navitoclax binds to and inhibits antiapoptotic B-cell lymphoma-2 (BCL-2) family proteins with high affinity. Thus, it selectively induces program death in cells that have a BCL-2 protein ratio shifted towards survival as observed in human cell lines derived from small cell lung carcinomas and lymphoid malignancies. Additionally, navitoclax potently enhances the cytotoxicity of both chemotherapy and radiation in cells derived from multiple, major tumor types, regardless of whether single-agent efficacy is achieved. Preclinical data suggest that the combination of navitoclax and ruxolitinib may provide disease-modifying therapy in subjects with primary and secondary MF. Preliminary clinical data from Study M16-109 of navitoclax and ruxolitinib in subjects with primary and secondary MF who have previously received ruxolitinib suggest favorable spleen response rates and an acceptable safety profile. Best on study spleen volume reductions of > 35% have been observed in 43% of subjects, with 35% of subjects also achieving a reduction of > 50% in total symptom scores. The response rates of the combination of navitoclax and ruxolitinib in subjects previously treated with ruxolitinib are comparable to those observed with both ruxolitinib and fedratinib in patients who were not previously treated. This double-blind, Phase 3 study will evaluate the combination of navitoclax and ruxolitinib versus ruxolitinib in adult subjects with primary or secondary MF who have not previously received a Janus kinase 2 (JAK2) inhibitor.
Objective(s) and Endpoint(s):	**Objectives** The primary objective is to evaluate the effect of navitoclax in combination with ruxolitinib on splenomegaly response when compared to ruxolitinib in subjects with MF. The secondary objectives are: • To evaluate the effect of navitoclax in combination with ruxolitinib on the onset, magnitude, and duration of disease response, including total symptom score (TSS), effects on spleen, bone marrow fibrosis, and anemia. • To evaluate the effect of navitoclax in combination with ruxolitinib on measures of health-related quality of life (HRQoL), including fatigue, and physical functioning. • To evaluate the effect of navitoclax in combination with ruxolitinib on overall survival (OS) and leukemia-free survival (LFS).

	The exploratory objectives are: • To evaluate responses to navitoclax and ruxolitinib versus ruxolitinib in subjects with high molecular risk (HMR) mutations. • To evaluate the effect of navitoclax in combination with ruxolitinib on progression-free survival (PFS). • To evaluate the effect of navitoclax in combination with ruxolitinib on the frequency of mutated alleles. • Exploration of biomarkers predictive of navitoclax activity and response may be performed. Potential analysis may include, but will not be limited to, the evaluation of: • BCL-2 family profiling • Inflammatory cytokine reduction • Mutational status. **Endpoints** Primary Efficacy Endpoint: • At least 35% reduction in spleen volume at Week 24 from baseline (SVR_{35W24}) as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria. Secondary Efficacy Endpoints: • Change in total symptom score (TSS) at Week 24 from baseline as measured by Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 • At least 35% reduction in spleen volume from baseline (SVR_{35}) as measured by MRI or CT scan, per IWG criteria • Duration of SVR_{35} • Change in fatigue at Week 24 from baseline as measured by the PROMIS Fatigue SF 7a • Change in physical functioning at Week 24 from baseline, as measured by the Physical functioning domain of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire (QLQ)-C30 • Anemia response per IWG criteria • Overall survival • Leukemia-free survival • Reduction in grade of bone marrow fibrosis from baseline as measured by the European consensus grading system Exploratory Endpoints: • At least 50% reduction in palpable splenomegaly from baseline per IWG criteria • Red blood cell (RBC) transfusion during study drug treatment

	• Change in quality of life from baseline as measured by the global health status/quality of life domain of the EORTC QLQ-C30 • Change in the summary score for the EORTC QLQ-C30 from baseline • Progression-free survival per IWG criteria • Change in frequency of allelic mutations from baseline • Change in EQ-5D-5L from baseline • Change in impacts associated with fatigue from baseline as assessed by the PROMIS Fatigue 7a impact items • Change in fatigue-related symptoms from baseline as assessed by the PROMIS Fatigue 7a symptom items • Translational biomarkers and correlation with clinical outcomes • Overall response of clinical improvement per IWG criteria • At least 50% reduction in TSS at Week 24 from baseline (TSS_{50W24}) • Time to first TSS_{50} • Duration of TSS_{50} • TSS response rate at any time based on meaningful change threshold (MCT) • Time to first TSS response • Duration of TSS response <u>Safety Endpoints:</u> Safety endpoints will be based on the following evaluations: adverse event (AE) monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG) variables, and clinical laboratory testing (hematology and chemistry). <u>Pharmacokinetic Endpoints:</u> Sparse pharmacokinetic (PK) samples will be collected at specified time points. Individual plasma concentrations of navitoclax from sparse PK sampling will be tabulated and summarized. Population PK parameters of navitoclax such as apparent oral clearance (CL/F) and apparent volume of distribution (V/F) may be estimated using non-linear mixed effects model. <u>Biomarker Endpoints:</u> Biospecimens (whole blood, plasma, bone marrow aspirate, and/or bone marrow core) will be collected at specified time points throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites. Some of these samples may be optional. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to mutational status, BCL-2 family profiling, and inflammatory cytokine reduction.

Investigator(s):	Multicenter
Study Site(s):	Approximately 190 sites in approximately 26 countries
Study Population and Number of Subjects to be Enrolled:	Approximately 230 adult subjects with intermediate-2 or high-risk MF who have not been previously treated with JAK2 inhibitor therapy.
Investigational Plan:	This is a Phase 3, double-blind, placebo-controlled, randomized, 2-arm study of the combination of navitoclax and ruxolitinib compared to ruxolitinib in subjects with MF who have not previously received JAK2 inhibitors. Approximately 230 subjects will receive either navitoclax once daily and ruxolitinib twice daily (Arm A), or placebo once daily and ruxolitinib twice daily (Arm B, control) until end of clinical benefit or occurrence of unacceptable toxicity or discontinuation criteria have been met. Stratification will be based on intermediate-2 versus high risk (Dynamic International Prognostic Scoring System Plus [DIPSS+]) and platelet count ≤ 200 × 10^9/L versus > 200 × 10^9/L.
Key Eligibility Criteria:	• Subject ≥ 18 years of age. • Subject with a documented diagnosis of primary MF as defined by the World Health Organization classification or secondary MF (post polycythemia vera [PPV]-MF or post essential thrombocythemia [PET]-MF) • Subject must be able to complete the MFSAF v4.0 on at least 4 out of the 7 days immediately preceding the date of randomization. • Subject has at least 2 symptoms with a score ≥ 3 or a total score of ≥ 12, as measured by the MFSAF v4.0. • Subject classified as intermediate-2 or high-risk MF as defined by the Dynamic International Prognostic Scoring System Plus (DIPSS+). • Subject must not have received prior treatment with a JAK2 inhibitor. • Subject must not have received prior treatment with a B-cell lymphoma 2 homology 3 (BH3) -mimetic compound, bromodomain and extra-terminal motif (BET) inhibitor or stem cell transplant. • Subject has splenomegaly defined as spleen palpation measurement ≥ 5 cm below costal margin or spleen volume ≥ 450 cm^3 as assessed centrally by MRI or CT scan. • Subject must be ineligible for stem cell transplantation at time of study entry due to age, comorbidities, or unfit for unrelated or unmatched donor transplant and other criteria per National Comprehensive Cancer Network guidelines. • Subject with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. • Subject must not receive medication that interferes with coagulation or platelet function within 3 days prior to the first

	dose of study drug or during the study treatment period except for low dose aspirin (up to 100 mg daily) and low molecular weight heparin (LMWH).

Study Drug and Duration of Treatment:	Navitoclax/placebo will be provided as film-coated tablets (25 mg and 100 mg) for oral administration. Ruxolitinib tablets will be provided by AbbVie or sourced locally by the sites, depending on country regulations.
	• **Arm A - Experimental group:** navitoclax + ruxolitinib
	• **Arm B – Control group:** placebo to match navitoclax + ruxolitinib
	Dosing of study drugs:
	• Navitoclax/placebo:
	  • Platelet count > 150 × 10^9/L: 200 mg once daily starting dose
	  • Platelet count ≤ 150 × 10^9/L: 100 mg once daily starting dose; escalate to 200 mg once daily after ≥ 7 days, if tolerable (platelets ≥ 75 × 10^9/L).
	  • After the Week 25 Day 1 visit, dose may be increased to 300 mg once daily at the discretion of the investigator based on platelet count for subjects with sub-optimal spleen response defined as failure to achieve a spleen volume reduction of at least 10%.
	• Ruxolitinib (administered per USPI/SmPC/local prescribing guidance):
	  • Platelet count > 200 × 10^9/L: 20 mg twice daily starting dose
	  • Platelet count 100 × 10^9/L to 200 × 10^9/L: 15 mg twice daily starting dose.
	  • Ruxolitinib dose adjustment in subjects with hepatic or renal impairment should be determined per local label/prescribing guidance.
	Treatment may continue until end of clinical benefit or occurrence of unacceptable toxicity or discontinuation criteria have been met.

Date of Protocol Synopsis:	23 March 2023

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Myelofibrosis (MF) is an acquired clonal Philadelphia chromosome negative myeloproliferative neoplasm that is characterized by constitutional symptoms, splenomegaly, an increased risk of transformation to acute myeloid leukemia, and a shortened life expectancy.[1] Although Janus kinase 2 (JAK2) inhibitors such as ruxolitinib are approved in several geographic regions, these therapies are insufficient for most patients and better treatments are needed. Whilst therapy with ruxolitinib induces improvement in splenomegaly and disease-related symptoms, it does not eradicate the malignant clones and may induce modest improvement in the degree of bone marrow fibrosis in a small subset of patients treated.[2,3] Patients who stop ruxolitinib rapidly become symptomatic, some patients do not respond to ruxolitinib, and others develop secondary resistance, thus ruxolitinib alone is typically insufficient for sustained disease control.[4] Current therapies, other than hematopoietic stem cell transplantation (HSCT) which is only accessible to 5 to 10% of patients, are not able to control all the clinical manifestations of MF. Therefore, new treatments including combination therapies with ruxolitinib as the backbone may provide additional benefits and improve clinical outcomes in these patients.

Navitoclax binds to and inhibits antiapoptotic B-cell lymphoma-2 (BCL-2) family proteins with high affinity to BCL-X_L, BCL-2 and BCL-W. Thus, it selectively induces program death in cells that have a BCL-2 family protein ratio shifted towards survival as observed in human cell lines derived from small cell lung carcinomas and lymphoid malignancies (concentration required for 50% effect [EC_{50}] ≤ 1 µM). Additionally, navitoclax potently enhances the cytotoxicity of both chemotherapy and radiation in cells derived from multiple, major tumor types, regardless of whether single-agent efficacy is achieved.

Clinical studies conducted to date have assessed safety, pharmacokinetics, and initial efficacy of navitoclax as a single agent and as combination therapy in subjects with hematological malignancies and subjects with solid tumors. The monotherapy recommended Phase 2 dose (RPTD) has been determined as 250 mg in chronic lymphocytic leukemia (CLL) (with a 100 mg lead-in period prior to Cycle 1) and 325 mg under the continuous dosing schedule in small cell lung cancer and other lymphoid malignancies (excluding CLL; with a 150 mg lead-in period prior to Cycle 1), although the starting dose was reduced to 250 mg in lymphoid malignancies as this was found to be more tolerable.[5-8]

Preclinical data suggest that navitoclax may overcome JAK2 resistance, resensitizing cells to JAK2 inhibition from ruxolitinib, and therefore may provide disease-modifying therapy in subjects with primary myelofibrosis (PMF) and secondary myelofibrosis (SMF).[6] The combination of navitoclax and ruxolitinib in subjects with MF (Study M16-109) has demonstrated efficacy in subjects with persistent splenomegaly while receiving treatment with ruxolitinib for at least 12 weeks (AbbVie data on file). The median duration of prior ruxolitinib exposure before initiating navitoclax on Study M16-109 was 21 months (range 4 to 71 months). After 24 weeks of treatment with navitoclax and ruxolitinib, 30% of subjects achieved spleen volume reduction ≥ 35% (SVR_{35}). Additionally, spleen responses seem to deepen beyond 24 weeks of treatment, and the best overall SVR_{35} was further improved to 43%. Symptom improvements were reported in 65% of subjects with 35% of subjects achieving ≥ 50%

reduction from baseline in total symptom score at Week 24. Additionally, reductions in bone marrow fibrosis of ≥ 1 grade were observed in 27% of subjects, suggesting this drug combination may be disease modifying. The safety profile was acceptable with the most common Grade ≥ 3 treatment-emergent AEs reported as thrombocytopenia and anemia. There were no serious adverse events of bleeding. There was 1 treatment-emergent death due to pneumonia that was assessed by the investigator as having no reasonable possibility of relationship to navitoclax.

Preliminary pharmacokinetic (PK) data from the Phase 2 M16-109 study of the combination of navitoclax and ruxolitinib in subjects with PMF and SMF who have previously received ruxolitinib showed that upon co-administration, navitoclax exposures (n = 34) were comparable to historical data in non-MF patient population, while ruxolitinib area under the curve from 0 to 12 hours (AUC_{0-12}) (n = 28) was 29% lower compared to historical data in MF patients. The impact of navitoclax on ruxolitinib exposures is being evaluated in Study M16-109.

Preliminary data in the Phase 2 M16-109 study of the combination of navitoclax and ruxolitinib in subjects with PMF and SMF who have previously received ruxolitinib suggest favorable spleen response rates and an acceptable safety profile. Best on study spleen volume reductions of > 35% have been observed in 43% of subjects, with 35% of subjects also achieving a reduction of > 50% in total symptom scores.[9] The response rates of the combination of navitoclax and ruxolitinib in subjects previously treated with ruxolitinib are comparable to those observed with both ruxolitinib and fedratinib in patients not previously treated.[2] These data support further evaluation of this combination in patients with MF that have not received prior treatment with a JAK2 inhibitor. This Phase 3 study is designed to evaluate the combination of navitoclax and ruxolitinib versus ruxolitinib in subjects with PMF or SMF who have not previously received a JAK2 inhibitor.

Clinical Hypothesis

Navitoclax, when combined with ruxolitinib, is reasonably likely to result in higher SVR_{35} rates that are more durable, greater reductions in total symptom score (TSS), reversal of bone marrow fibrosis, and more allelic burden reductions than the current standard treatment, ruxolitinib alone.

2.2 Benefits and Risks to Subjects

Ruxolitinib (a dual Janus kinase 1 [JAK1] and JAK2 inhibitor) and fedratinib (dual JAK2 and FMS-like tyrosine kinase 3 [FLT3] inhibitor) are approved by numerous regulatory bodies worldwide for the treatment of myelofibrosis. While the approval of these JAK2 inhibitors has changed the treatment landscape for patients with myelofibrosis, their therapeutic remit is aimed at improving symptoms and quality of life. The only treatment modality capable of curing MF is allogenic HSCT. The applicability of HSCT is limited by the inherent risks in this population, with their attendant comorbidities.

Preclinical data suggest that the combination of navitoclax with ruxolitinib may provide disease-modifying therapy for patients with PMF or SMF. Clinical studies (single-agent and combination therapy) have assessed the safety, pharmacokinetics and initial efficacy in subjects with hematologic malignancies or in subject with solid tumors.

Risks observed in nonclinical and/or clinical studies associated with navitoclax administration are thrombocytopenia, lymphopenia, and neutropenia. Thrombocytopenia has been the primary

dose-limiting toxicity. Navitoclax accelerates apoptosis, rather than lysis, of circulating mature platelets whether endogenous or transfused. This mechanism of action differs from the thrombocytopenia caused by conventional chemotherapy (i.e., toxicity to platelets progenitors in the bone marrow) and should, therefore, be managed. Actions are in place in study protocols to mitigate these risks and, when medically indicated, to treat these effects; these include appropriate patient selection, careful monitoring, and treatment management guidelines.

The most common treatment emergent hematological adverse reactions of any grade with an incidence > 10% reported with navitoclax in combination with ruxolitinib (Study M16-109; Cohort 3) in patients with MF who have not previously received ruxolitinib are thrombocytopenia, neutropenia, and anemia. The most common treatment emergent nonhematological adverse reactions of any grade with an incidence ≥ 10% are nausea and diarrhea.

The most common hematological adverse reactions with an incidence > 20% reported with ruxolitinib monotherapy in patients treated for MF are thrombocytopenia and anemia. The most common nonhematological adverse reactions with an incidence ≥ 15% are bruising, dizziness, headache, and diarrhea. Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have also been reported requiring periodic skin examination.

The preliminary data of the combination of navitoclax and ruxolitinib (Study M16-109) in patients with MF who have previously received ruxolitinib for at least 12 weeks with persistent splenomegaly are favorable, demonstrating improvement in spleen volume reduction and total symptom score along with reduction in bone marrow fibrosis after treatment with current standard of care, and support further evaluation of the combination in patients with MF who have not received prior treatment with a JAK2 inhibitor.

The Sponsor has evaluated the potential risks of study participation during a global or regional epidemic or other extreme circumstance and concludes that the potential benefit of the study treatment outweighs the additional risk.

For further benefit and risk details, please see the current navitoclax Investigator's Brochure.

Considering the coronavirus disease 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Subjects receiving navitoclax may be at an increased risk for COVID-19 infection or experience serious illness if infected. Management of these adverse events will be made on a case-by-case basis with consideration of benefit/risk by the investigators. However, based on the population, the disease being studied, and the anticipation that COVID-19 related risks are unknown between study subjects and the broader population of subjects receiving treatment for myeloproliferative neoplasms, no known change to the benefit/risk balance for subjects in this study is expected.

3 OBJECTIVES AND ENDPOINTS

Primary Objective

1. To evaluate the effect of navitoclax in combination with ruxolitinib on splenomegaly response when compared to ruxolitinib in subjects with myelofibrosis (MF).

Secondary Objectives

1. To evaluate the effect of navitoclax in combination with ruxolitinib on the onset, magnitude, and duration of disease response, including total symptom score (TSS), effects on spleen, bone marrow fibrosis, and anemia.
2. To evaluate the effect of navitoclax in combination with ruxolitinib on measures of health-related quality of life (HRQoL) including fatigue, and physical functioning.
3. To evaluate the effect of navitoclax in combination with ruxolitinib on overall survival (OS) and leukemia-free survival (LFS).

Exploratory Objectives

1. To evaluate responses to navitoclax and ruxolitinib in subjects with high molecular risk (HMR) mutations.
2. To evaluate the effect of navitoclax in combination with ruxolitinib on progression-free survival (PFS).
3. To evaluate the effect of navitoclax in combination with ruxolitinib on the frequency of mutated alleles.
4. Exploration of biomarkers predictive of navitoclax activity and response may be performed. Potential analysis may include, but will not be limited to, the evaluation of:
    - BCL-2 family profiling
    - Inflammatory cytokine reduction
    - Mutational status.

3.1 Primary Endpoint

At least 35% reduction in spleen volume at Week 24 (SVR_{35W24}) from baseline as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.[9]

3.2 Secondary Endpoints

Secondary efficacy endpoints:

- Change in total symptom score (TSS) at Week 24 from baseline as measured by Myelofibrosis Symptom Assessment Form (MFSAF) v4.0
- At least 35% reduction in spleen volume from baseline (SVR_{35}) as measured by MRI or CT scan, per IWG criteria
- Duration of SVR_{35}
- Change in fatigue at Week 24 from baseline, as measured by the PROMIS Fatigue SF 7a

- Change in physical functioning at Week 24 from baseline, as measured by the physical functioning domain of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30
- Anemia response per IWG criteria
- Overall survival
- Leukemia-free survival
- Reduction in grade of bone marrow fibrosis from baseline as measured by the European consensus grading system[10]

3.3 Exploratory Endpoints

Exploratory endpoints:

- At least 50% reduction in palpable splenomegaly from baseline per IWG criteria
- Red blood cell (RBC) transfusion during study drug treatment
- Change in quality of life from baseline as measured by the global health status/quality of life domain of the EORTC QLQ-C30
- Change in the summary score for the EORTC QLQ-C30 from baseline
- Progression-free survival (PFS) per IWG criteria
- Change in frequency of allelic mutations from baseline
- Change in EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L) from baseline
- Change in fatigue-related symptoms from baseline as assessed by the PROMIS Fatigue 7a symptom items
- Change in impacts associated with fatigue from baseline as assessed by the PROMIS Fatigue 7a impact items.
- Translational biomarkers and correlation with clinical outcomes.
- Overall response of clinical improvement per IWG criteria
- At least 50% reduction in TSS at Week 24 from baseline (TSS_{50W24})
- Time to first TSS_{50}
- Duration of TSS_{50}
- TSS response rate at any time based on meaningful change threshold (MCT)
- Time to first TSS response
- Duration of TSS response

3.4 Safety Endpoints

The safety endpoints will be based on the following evaluations:

- Adverse event (AE) monitoring
- Physical examinations
- Vital sign measurements
- Electrocardiogram (ECG) variables
- Clinical laboratory testing (hematology and chemistry).

3.5 Pharmacokinetic Endpoints

Sparse PK samples will be collected at specified time points (see study activities table in Appendix D). Individual plasma concentrations of navitoclax and possible metabolite(s) from sparse PK sampling will be tabulated and summarized. Population PK parameters of navitoclax such as apparent oral clearance (CL/F) and apparent volume of distribution (V/F) may be estimated using non-linear mixed effects model.

Further details regarding PK sampling are provided in the Operations Manual, Section 3.7.

3.6 Biomarker Research Endpoints

Biospecimens (whole blood, plasma, bone marrow aspirate, and/or bone marrow core) will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites. Some of these samples may be optional. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to: mutational status, BCL-2 family profiling, and inflammatory cytokine reduction. This research may be exploratory in nature and the results may not be included with the clinical study report.

Further details regarding the biomarker research rationale and collection time points are located in Appendix D and the Operations Manual, Section 3.8.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3, double-blind, placebo-controlled, randomized, 2-arm study evaluating the efficacy and safety of the combination of navitoclax and ruxolitinib compared to ruxolitinib, in subjects with intermediate-2 or high-risk MF. The target population comprises adult subjects with MF who have not been previously treated with JAK2 inhibitor therapy with measurable splenomegaly and are not candidates for allogenic-stem cell transplantation.

Approximately 230 subjects will be enrolled. Subjects will be randomized in a 1:1 ratio to one of the following treatment arms, with stratification factors of intermediate-2 versus high risk (Dynamic International Prognostic Scoring System Plus [DIPSS+])[11] and platelet count ≤ 200 × 10^9/L versus > 200 × 10^9/L:

- **Arm A – Experimental group:** navitoclax + ruxolitinib
- **Arm B – Control group:** placebo to match navitoclax + ruxolitinib

Dosing of study drugs:

- Navitoclax/placebo:
  - Platelet count > 150 × 10^9/L: 200 mg once daily starting dose
  - Platelet count ≤ 150 × 10^9/L: 100 mg once daily starting dose; escalate to 200 mg once daily after ≥ 7 days, if tolerable (platelets ≥ 75 × 10^9/L).
  - After the Week 25 Day 1 visit, dose may be increased to 300 mg once daily at the discretion of the investigator based on platelet count for subjects with sub-optimal spleen response defined as failure to achieve a spleen volume reduction of at least 10%.
- Ruxolitinib (administered per USPI/SmPC/local prescribing guidance):
  - Platelet count > 200 × 10^9/L: 20 mg twice daily starting dose
  - Platelet count 100 × 10^9/L to 200 × 10^9/L: 15 mg twice daily starting dose.
  - Ruxolitinib dose adjustment in subjects with hepatic or renal impairment should be determined per local label/prescribing guidance.

Ruxolitinib and navitoclax/placebo will be administered beginning on Day 1 at the individualized starting dose based on baseline platelet counts determined within 24 hours prior to the first dose. The starting dose of ruxolitinib may be adjusted at the discretion of the investigator, as medically appropriate in consultation with the AbbVie Therapeutic Area Medical Director/Scientific Director (TA MD/SD), with subsequent increase in dose as described in Table 1. Ruxolitinib and navitoclax/placebo dose reductions are permissible, as needed, for management of toxicities (Section 6.2).

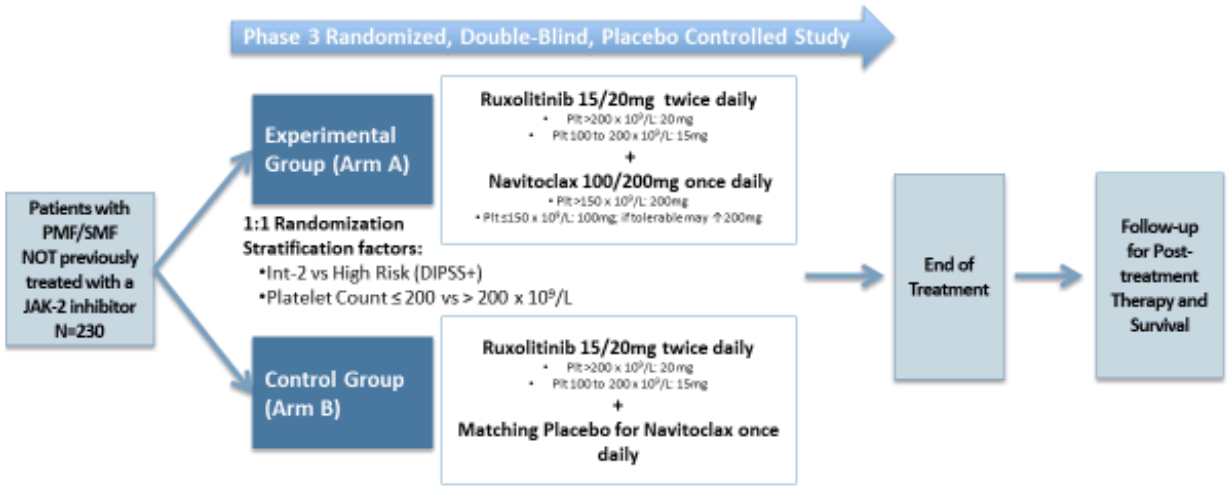
Treatment with study drugs may continue until end of clinical benefit or occurrence of unacceptable toxicity or discontinuation criteria have been met. At the end of study drug treatment, a treatment completion and 30-day safety visit will be conducted.

After documented disease progression or initiation of post-treatment cancer therapy, the subject will enter the survival follow-up phase.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual.

See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schema



DIPSS+ = Dynamic International Prognostic Scoring System Plus; Int = intermediate; Plt = platelet; PMF = primary myelofibrosis; SMF = secondary myelofibrosis

Option for Safety Lead-In Phase

The Sponsor plans to review safety data from at least 6 subjects administered navitoclax in combination with ruxolitinib for at least 8 weeks in either the frontline cohort of Study M16-109 or Study M16-191. If the review of safety data from Study M16-109 is not completed prior to dosing the 12th subject in Study M16-191, enrolment will be paused to complete independent data monitoring committee (IDMC) review of safety data from the first 12 subjects enrolled in Study M16-191.

4.2 Discussion of Study Design

Choice of Control Group

Ruxolitinib is the current standard treatment that is approved for patients with MF and induces improvement in splenomegaly and disease-related symptoms compared with placebo or best available therapy.[2] This study compares navitoclax in combination with ruxolitinib to placebo in combination with ruxolitinib. The choice of control group allows for a double-blind assessment of the contribution of navitoclax to the safety and efficacy of the backbone treatment of ruxolitinib.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with MF. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

JAK2 inhibition induces down-regulation of the anti-apoptotic protein myeloid cell leukemia 1 (MCL-1) suggesting a role for navitoclax, a BCL-XL inhibitor, in the treatment of myeloproliferative neoplasms including MF. Therefore, subjects diagnosed with MF (PMF or SMF) represent the target population for this study.

Selection of Doses in the Study

The recommended starting dose of ruxolitinib for MF is according to the approved label and is based on the subject's baseline platelet count determined within 24 hours prior to the first dose: 20 mg twice daily (> 200 × 10^9/L) or 15 mg twice daily (100 × 10^9/L to 200 × 10^9/L). The investigator may adjust the starting dose of ruxolitinib as medically appropriate after consultation with the AbbVie TA MD/SD, with subsequent increase in dose as shown in Table 1.

As a BCL-X_L inhibitor, navitoclax causes thrombocytopenia via intravascular apoptosis of platelets. AbbVie internal data indicate that the effect of navitoclax on platelet reduction is exposure-related but may be diminished upon continued administration. Accordingly, thrombocytopenia may occur with navitoclax upon exposure to sufficient navitoclax concentrations. Additionally, thrombocytopenia and anemia are the primary reasons for ruxolitinib dose reductions.[12]

Preliminary data from Study M16-109 showed that weekly navitoclax dose escalation from 50 mg once daily to 300 mg once daily in combination with ruxolitinib at ≥ 10 mg, as was initially tested in Study M16-109, was generally safe without clinically relevant thrombocytopenia-related bleeding. In Study M16-109, 83% of subjects experienced a dose reduction of navitoclax during study treatment with the primary reason being thrombocytopenia. Of the subjects with navitoclax dose reductions for thrombocytopenia, 60% received 300 mg of navitoclax. Therefore, doses of navitoclax < 300 mg once daily seem to be better tolerated in patients with MF.

In addition, a mechanistic PK/PD model was used to evaluate the effect of navitoclax and ruxolitinib on platelets counts. The model incorporated different mechanisms by which navitoclax and ruxolitinib cause thrombocytopenia (navitoclax by peripheral platelet apoptosis and ruxolitinib by slowing platelet production). Simulations were conducted at:

- Different starting doses of navitoclax (100 to 300 mg once daily)
- Starting at 100 mg once daily with a weekly ramp-up to 200 mg once daily

Simulations indicate that the maximum decreases in platelet count and incidences of Grade 3/4 thrombocytopenia for the weekly ramp-up from 100 to 200 mg once daily were either similar to or slightly lower than those predicted at a flat starting dose of 200 mg (up to 5% difference).

The proposed starting dose of navitoclax in combination with ruxolitinib is 200 mg once daily or 100 mg once daily based on platelet counts determined pre-dose within 24 hours of first dose. To minimize the risk of relevant thrombocytopenia, AbbVie has proposed a lower starting dose of 100 mg once daily for subjects with a baseline platelet count ≤ 150 × 10^9/L. For subjects with a baseline platelet count of ≤ 150 × 10^9/L, the dose of navitoclax will be increased to 200 mg once daily after approximately 7 or more days, provided the platelet count remains ≥ 75 × 10^9/L. After the Week 25 Day 1 disease

assessment, navitoclax /placebo dose may be increased to 300 mg once daily at the discretion of the investigator based on platelet count for subjects with sub-optimal spleen response defined as failure to achieve a spleen volume reduction of at least 10%.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects must voluntarily sign and date an informed consent (or their legally authorized representative can sign and date the informed consent upon subject's understanding of the consent, if permitted by local regulations), approved by an independent ethics committee (IEC)/institutional review board (IRB) prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Subjects ≥ 18 years of age.
- 3. Subject must be able to complete the MFSAF v4.0 on at least 4 out of the 7 days immediately preceding the date of randomization.
  - Subject has at least 2 symptoms with a score ≥ 3 or a total score of ≥ 12, as measured by the MFSAF v4.0.
- 4. Subject must meet the following laboratory criteria per local laboratory reference range at Screening:
  - Adequate bone marrow reserve; in the absence of growth factors, thrombopoietic factors, or platelet transfusions for at least 14 days prior to Week 1 Day 1.
    - Platelet count ≥ 100×10^9/L
    - Absolute neutrophil count (ANC) ≥ 1×10^9/L.
  - Renal function: calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault formula.
  - Hepatic function and enzymes:
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × upper limit of normal (ULN)
    - Total bilirubin ≤ 1.5 × ULN (exception: subjects with Gilbert's Syndrome may have total bilirubin > 1.5 × ULN)
    - Coagulation: activated partial thromboplastin time (aPTT) and prothrombin time (PT) or international normalized ratio (INR) ≤ 1.5 × ULN.

- 5. Subject is willing and able to comply with procedures required in this protocol.

Disease Activity

- 6. Subject with a documented diagnosis of PMF as defined by the World Health Organization classification[11] or SMF (post polycythemia vera [PPV]-MF or post essential thrombocythemia [PET] – MF).
- 7. Subject classified as intermediate-2 or high-risk MF as defined by the DIPSS+ (Appendix F).[13]
- 8. Subject must not have received prior treatment with a JAK2 inhibitor.
- 9. Subject must not have received prior treatment with a B-cell lymphoma 2 homology 3 (BH3) mimetic compound or bromodomain and extra-terminal motif (BET) inhibitor or allogeneic stem cell transplant.
- 10. Subject has splenomegaly defined as spleen palpation measurement ≥ 5 cm below costal margin or spleen volume ≥ 450 cm^3 as assessed centrally by MRI or CT scan.
- 11. Subject must be ineligible for stem cell transplantation at time of study entry due to age, comorbidities, or unfit for unrelated or unmatched donor transplant and other criteria per National Comprehensive Cancer Network guidelines.[14]
- 12. Subject must not have received splenic irradiation within 6 months prior to the Screening Visit or had a prior splenectomy.
- 13. Subject must not have leukemic transformation, defined as > 10% blasts in peripheral blood or bone marrow.
- 14. Subject with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Subject History

- 15. Subject must not have cardiovascular, endocrinologic, hepatic, immunologic, metabolic, neurologic, psychiatric, pulmonary, renal disease, or any other condition that, in the opinion of the investigator, could adversely affect the subject's participation in this study (including the capacity to provide consent) or the interpretation of study results.
- 16. Subject must not have history of an active malignancy other than MF within 2 years prior to Screening, except for:
  - Adequately treated in-situ carcinoma of the cervix
  - Adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin
  - Asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy
  - Adequately treated in-situ carcinoma of esophagus or gastric mucosa.
- 17. Subject must not have known human immunodeficiency virus (HIV) infection. Note: HIV testing does not need to be conducted at Screening unless it is required per local guidelines or institutional standards.

- 18. Subject must not have known hepatitis B (HBV) or hepatitis C (HCV) infection requiring treatment. Subjects with an undetectable viral load within 3 months of Screening and those with serologic evidence of prior vaccination to HBV (i.e., HBs antigen [Ag-], and anti-HBs+) may participate. (Hepatitis B or C testing is not required at Screening unless it is required per local guidelines or institutional standards).
- 19. Subject must have a negative tuberculin skin test (purified protein derivative, PPD) and/or interferon-gamma release assay (IGRA), or any approved test per local guidelines, or have no evidence of latent tuberculosis (TB) prior to enrollment.
- 20. Subject must not have any clinically significant, uncontrolled medical conditions including, but not limited to:
  - Ongoing systemic infection (viral, bacterial, mycobacterial, or fungal)
  - Febrile neutropenia.
- 21. No history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 22. No clinically relevant or significant ECG abnormalities, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's formula (QTcF) > 450 msec (males) or > 470 msec (females).
- 23. No known active SARS-CoV-2 infection. Subjects must not have signs/symptoms associated with SARS-COV-2 infection or known exposure to a confirmed case of SARS-CoV-2 infection during the 14 days prior to Screening.

  Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 viral clearance criteria:

  - Symptomatic subjects: At least 2 consecutive negative viral tests ≥ 24 hours apart conducted at least 10 days after resolution of symptoms, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath).
  - Asymptomatic subjects (if acceptable locally): At least 2 consecutive negative viral tests ≥ 24 hours apart conducted at least 10 days after the prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects).

  Frequency or timing of SARS-CoV-2 testing and the interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity, and local/institutional guidelines.

Contraception

- 24. For all females of child-bearing potential; a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.
- 25. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control, that is effective from Study Day 1 through at least 30 days after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.

- 26. If female, not pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
- 27. If male, and subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 90 days after the last dose of study drug, to practice the protocol-specified contraception.
- 28. If male not considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug.

Concomitant Medications

- 29. Subject must not receive anticancer therapy for another active malignancy or MF, including chemotherapy, radiation therapy, hormonal therapy (with the exception of hormones for thyroid conditions or estrogen replacement therapy) within 30 days, or hydroxyurea or other supportive medication used for cytoreduction, or steroid therapy for myelofibrosis or for anti-neoplastic intent within 7 days, prior to first dose of study drug, and during the study drug treatment period.
- 30. Subject must not receive medication that interferes with coagulation or platelet function within 3 days prior to the first dose of study drug or during the study drug treatment period, except for low dose aspirin (up to 100 mg daily) and low molecular weight heparin (LMWH).
- 31. Subject must not receive biologics for MF within 30 days prior to the first dose of study drug and during navitoclax and ruxolitinib administration.
- 32. Subject must not have received any live vaccine within 4 weeks prior to the first dose of study drug, or be expected to need of live vaccination during study participation including at least 4 weeks after the last dose of study drug.
- 33. Subject must not have been treated with any investigational drug within 30 days prior to the first dose of study drug, or currently be enrolled in another clinical study, or another research study except for observational studies with collection of demographic data.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 30 days after the last dose of study drug.
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
- If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential, must agree **to use condoms, even if the male subject has undergone a successful vasectomy**, from Study Day 1 through at least 90 days after the last dose of study drug:

- His female partner(s) must also use at least 1 of the following methods of birth control:
  - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline Day 1

- bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
- intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy, and is the sole sexual partner of the trial subject)

5.3 Prohibited/Cautionary Medications and Therapy

Anti-cancer therapy for another active malignancy or MF including chemotherapy, immunotherapy, radiotherapy, hormonal therapy (with the exception of hormones for thyroid conditions or estrogen replacement therapy), and other investigational agents are not allowed during study drug treatment. Treatment with supportive medications for MF such as interferon, erythropoietin, danazol, and steroids, is not permitted during study drug treatment. Steroid therapy for MF or for anti-neoplastic intent will not be allowed within 7 days prior to the first dose of study treatment or during study drug treatment. If medically indicated, allowed steroid therapy includes inhalational steroids for the treatment of asthma or chronic obstructive pulmonary disease, topical steroids, and steroids for prevention and/or treatment of transfusion related reactions. Steroids for any other indications should be limited to lower dose and/or short duration.

Biologics for MF will not be allowed within 30 days prior to the first dose of study drug and during navitoclax/placebo or ruxolitinib administration.

Medication that interferes with coagulation or platelet function (e.g., warfarin, apixaban, clopidogrel, tirofiban, disulfiram [potential prolongation of PT]), except for low dose aspirin (up to 100 mg daily) and LMWH, are not allowed during study drug treatment. Dose adjustments for LMWH should be made based on the subject's platelet counts and the local label of the agent being used concomitantly.

Hydroxyurea or other medications used for cytoreduction should be discontinued 7 days prior to first dose of study drug and are not allowed during study drug treatment.

Janus kinase inhibitors for the treatment of inflammatory diseases are not permitted during study drug treatment.

Treatment with NSAIDs for limited duration is permitted during study treatment if platelet counts $>100 \times 10^9$/L.

Selective serotonin re-uptake inhibitors and serotonin and norepinephrine reuptake inhibitors (SSRIs and SNRIs; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine) are cautionary as they may increase the risk of bleeding events.

The following concomitant medications are cautionary during study drug treatment as they may potentially lead to drug-drug interaction(s). The investigator should assess whether a potential study subject is taking any of the medications in the categories described below and, if so, document the use of medications known or suspected to fall in the following medication categories:

- Strong cytochrome P450 (CYP) 3A inhibitors (e.g., ketoconazole and clarithromycin), and foods that inhibit CYP3A such as grapefruit and its juice, star fruit, and Seville oranges (due to possible inhibition of the metabolism of navitoclax).

  Ruxolitinib is predominantly metabolized by CYP3A4 and to a lesser extent by CYP2C9. For subjects who are taking strong CYP3A4 inhibitors (such as ketoconazole and clarithromycin) or fluconazole concurrently with study drug treatment, the local, approved ruxolitinib product label should be referenced for ruxolitinib dose reduction, interruption, and discontinuation, or monitoring guidelines.
- CYP2C8 substrates such as glitazones and select statins (due to expected inhibition of the metabolism of CYP2C8 substrates).
- CYP2C9 substrates such as phenytoin and tolbutamide (due to expected inhibition of the metabolism of CYP2C9 substrates).
- Strong CYP3A inducers such as rifampin and carbamazepine (due to possible induction of the metabolism of navitoclax). The local, approved ruxolitinib product label should be referenced for monitoring guidelines.
- P-glycoprotein (P-gp) substrates such as digoxin, and breast cancer resistance protein (BCRP) substrates such as rosuvastatin (due to possible inhibition of these transporters by navitoclax).
- Inhibitors and inducers of P-gp and BCRP (navitoclax is a substrate of P-gp and BCRP).
- The local, approved ruxolitinib product label should be referenced for monitoring guidelines when co-administered with CYP3A inducers or drugs transported by P-gp and BCRP.

A sample list of excluded and cautionary medications is provided in (Appendix G). Since a complete list of medications that should only be used with caution cannot be provided, please refer to the appropriate product label and/or contact the AbbVie TA MD/SD whether a specific concomitant medication falls into the above-mentioned categories. Information regarding potential drug interactions with navitoclax can also be located in the current navitoclax Investigator's Brochure.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded from the time of signing the consent form at Screening until the 30 days after the last dose of study medication.

Best supportive care and treatment is allowed for each subject, e.g., antiemetics, antibiotics, transfusions, nutritional support, pain control etc, with the exception of therapy and medications detailed in Section 5.3.

Colony stimulating factors (G-CSF, GM-CSF) are allowed during administration of navitoclax if deemed necessary by the investigator and if mutually agreed upon by AbbVie TA MD/SD.

Anti-herpes and anti-pneumocystis carinii/jiroveci pneumonia (PCP) prophylaxis should be considered if clinically indicated. Trimethoprim and sulfamethoxazole can be considered for PCP prophylaxis with

close clinical monitoring; whilst there is a potential for drug-drug interactions, any clinical effects are likely to be limited.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with navitoclax can be located in the navitoclax Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications as detailed in Section 5.1. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated. Investigators are to follow the prescribing information for the vaccine.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the investigator/treating physician and the subject.

The potential impact of navitoclax and ruxolitinib on SARS-CoV-2 vaccination is unknown. Therefore, the timing of administration of vaccine in relation to the study drug should be based on the investigator's medical assessment of the subject's disease. These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with MF and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any adverse events associated with the COVID-19 vaccine.

5.5 Subject Discontinuation from Study Drug Treatment and Discontinuation of Study

Treatment with study drug may continue until end of clinical benefit or occurrence of unacceptable toxicity or discontinuation from study. A subject may voluntarily withdraw or be withdrawn from study drug treatment at any time for reasons including, but not limited to, the following:

- The subject is no longer deriving clinical benefit from study drug treatment, has disease progression, or the investigator believes it is in the best interests of the subject.
- The subject requires alternative therapy for treatment of MF.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie TA MD.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.

- Introduction of prohibited medications and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug, or begins or intends breastfeeding.
- Significant subject noncompliance with study drug administration, study procedures, or study requirements, which would put the subject at risk for continued participation in the trial.
- The subject withdraws consent to receiving study drug treatment.
- Any other medical reason that AbbVie or the investigator deems appropriate.
- If the study treatment is unblinded by the investigator, that subject would need to be discontinued from study treatment and post-treatment or survival follow-up would commence.

Withdrawal from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up (this request must be documented in the subject's medical records and signed by the investigator)
- Lost to follow-up
- Death of subject
- Study termination by Sponsor.

Discussion with the TA MD/SD is recommended prior to discontinuation of a subject from study treatment for any reason other than described above to ensure all acceptable mitigation steps have been evaluated.

Subjects with disease progression or relapse may continue to receive study treatment if the investigator considers it to be in the best interest of the subject. Disease assessment per protocol criteria at the time of disease progression will be captured in EDC. The subject will be monitored per study procedures described in Appendix D. Activity Schedule or more often if the investigator considers it necessary.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. This study will be monitored regularly by AbbVie in addition to an independent data monitoring committee (IDMC). The study has a safety review plan to assess laboratory and adverse event data on a weekly basis and serious adverse events on a daily basis. An aggregate review of the blinded aggregated data will be conducted once every 3 months. The product safety team including cross functional members is responsible for the ongoing safety monitoring of the program, including recommendations to modify or discontinue the study for unanticipated safety events. The study may be terminated due to unfavorable risk benefit assessment or at the IDMC's recommendation based on safety or efficacy concerns. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator; the investigator must promptly notify any subjects enrolled in the study and arrange alternative therapy for MF.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual (Appendix I).

The investigator should contact the AbbVie TA MD/SD before discontinuing a subject from the study for a reason other than "planned per protocol" to ensure that all acceptable mitigation steps have been explored.

Refer to the Operations Manual (Appendix I) for details of how to handle activities/procedures.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

During the study drug dosing period, if a subject has a confirmed (viral test positive or symptomatic disease) or is suspected to have COVID-19, recommend study drug or placebo interruption until infection is considered resolved per local requirements/recommendations, based on either clinical course or laboratory SARS-CoV-2 testing results. If the investigator feels interrupting study drug or placebo during active COVID-19 infection is not in the subject's best interest, navitoclax or placebo dosing may be continued without interruption, in which case the TA MD/SD should be notified within 48 hours after this decision.

Ruxolitinib dosing may continue without changes or may be adjusted or interrupted, as determined by the investigator on a case-by-case basis, based on overall benefit/risk assessment including potential effects of reduced treatment intensity on underlying MF and/or risk of COVID-19-related sequelae. COVID-19 and MF treatment regimens should be assessed for drug-drug interactions and potential need for dose adjustments. Ruxolitinib dosing may be tapered when needed to avoid exacerbation of disease associated with abrupt interruption.

Per protocol, the investigator can temporarily interrupt study drug at any time for a safety issue, or for any reason if they feel that the risk outweighs the benefit of study treatment. Treatment interruption longer than 28 days must be discussed with the TA MD/SD.

Subjects should be reminded by the site staff to notify the investigator immediately if they develop any signs and symptoms of COVID-19 infection (e.g., fever, sweating, chills, feeling tired, cough, or shortness of breath).

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early. Subjects who discontinue study drug treatment should continue on study with all assessments conducted through post-treatment follow-up visits and survival follow up (per the Operations Manual, Section 2.2) until death, subject withdrawal from study participation (i.e., withdrawal of informed consent) or study termination, whichever occurs first.

If a subject withdraws from study follow up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn and no longer wishes biomarker samples research to continue, samples will not be analyzed, and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research before subject withdrawal of consent, will remain part of the study results.

5.7 Post-Treatment Follow Up

All subjects who discontinue study drug treatment after 24 weeks for reasons other than disease progression will return for post-treatment follow-up visits approximately every 12 weeks following the treatment completion visit to assess disease status until documented disease progression or leukemic transformation or initiation of post-treatment cancer therapy.

For subjects who discontinue study treatment prior to completing 24 weeks of study treatment without intervening new treatment for myelofibrosis and who do not have documented disease progression, disease response assessments, including MRI/CT scans, should be conducted per the visit schedule up to and including the Week 25 Day 1 visit. Once the Week 25 Day 1 disease response assessments are completed the subject will continue on study every 12 weeks in post-treatment follow up, or every 2 months in survival follow up, based on post-treatment status (i.e., subjects who achieve disease progression, have lost clinical benefit, or have started another treatment would move onto survival follow up).

5.8 Survival Follow Up

For all subjects, survival follow-up will be performed approximately every 2 months for up to 8 years after the last subject last dose (unless informed consent has been withdrawn for collection of such information; this request must be documented in the subject's source documentation and electronic case report form [eCRF]), or more frequently, as requested by the Sponsor to support data analyses. Survival information (date and cause of death, details of post-treatment cancer therapies including response and progression) may be collected via telephone calls (e.g., to subject or family member), clinic visits, and/or public database searches. If the subject withdraws from survival follow up, the study staff may use public information sources (e.g., public records, death certificates) to obtain information about survival status only, as appropriate per local regulations.

5.9 Study Drug

Navitoclax and matching placebo will be provided by the Sponsor as film-coated tablets (25 mg and 100 mg) for oral administration taken once daily in the morning. Tablets must be taken with water within approximately 30 minutes after the completion of a meal. Tablets must be swallowed whole and

must not be broken, chewed, or crushed. If the subject misses a dose of navitoclax/placebo, the missed dose should be taken with food and water within 8 hours of the scheduled dose time. After 8 hours, the missed dose should not be taken and the next dose of navitoclax/placebo will be at the next scheduled dosing time.

If the subject vomits following dosing, no additional dose should be taken that day. The next prescribed dose of navitoclax/placebo should be taken at the usual time the following day.

Ruxolitinib tablets will be provided by AbbVie or sourced locally by the sites, depending on country regulations. Ruxolitinib should be taken orally twice daily at approximately the same time each day, once in the morning (at the same time as navitoclax, if applicable) and once in the evening, approximately 12 hours later. The absorption of ruxolitinib is not affected by food and ruxolitinib may be taken with or without food. If the subject misses a dose of ruxolitinib, the subject should take the next dose at the scheduled time. The subject should not take 2 doses at the same time.

Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix I for details on DTP shipment of study drug.

Subjects will record the time of navitoclax/placebo dosing on a subject dosing diary for the 2 doses prior to the Week 2 Day 1, Week 3 Day 1, and Week 5 Day 1 visits. Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. Study site personnel will document the containers and number of tablets returned.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug/device accountability procedures.

Further information on study drug, packaging, labeling, etc., is provided in the Operation Manual, Section 6.

5.10 Randomization/Drug Assignment

Interactive Response Technology (IRT) will be utilized to register (screen and randomize) subjects on study. The site will contact the IRT to obtain a screening (subject) number only after the subject has signed the informed consent and prior to any study-specific procedures being performed (e.g., labs are drawn). Subjects who satisfy all eligibility criteria at Screening will proceed to being randomized based

on baseline platelet counts determined within 24 hours prior to the first dose. The site will contact the IRT to complete the randomization process and obtain study drug assignment.

The IRT will randomize subjects into 2 treatment arms using 1:1 randomization ratio. Randomization will be stratified by:

- Intermediate-2 versus high risk (DIPSS+)
- Platelet count ≤ 200 × 10^9/L versus > 200 × 10^9/L (determined within 24 hours prior to first dose)

Blinding of Investigational Product

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the navitoclax film-coated tablets and placebo-film-coated tablets provided for the study will be identical in appearance.

The IRT will provide access to unblinded subject treatment information in the case of a medical emergency. AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

5.11 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

5.12 Data Monitoring Committee

An IDMC will regularly review unblinded safety data from the ongoing study, once every 6 months, according to the schedule provided in the IDMC charter, including adverse events and laboratory results. The unblinded safety analyses will be performed by an independent statistical data analysis center (SDAC) external to AbbVie and reviewed by the IDMC. AbbVie personnel will remain blinded and will not have access to the unblinded analyses prepared for the IDMC. The IDMC will provide recommendations to AbbVie as per the IDMC charter including any modifications to the protocol or discontinuations of the study.

A separate IDMC charter will be prepared outside of the protocol that will further describe the IDMC membership (which will include individuals with experience in treatment of patients with myeloproliferative neoplasms), roles and responsibilities of the IDMC members, frequency and scope of the data reviews, and expectations for blinded communications.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations," such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an adverse event or not. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening of disease under study or underlying cancer (serious or nonserious event) should be collected as an adverse event due to disease progression on the eCRF. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be adverse events.

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. All adverse events will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event. Hospitalization for the purpose of monitoring platelet counts post study drug administration is not considered an adverse event or serious adverse event. If the hospitalization is prolonged due to an event not related to monitoring platelet counts, then adverse event/serious adverse event criteria is to be assessed.

If an adverse event, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious adverse event within 24 hours of the site being made aware of the serious adverse event (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 30 days after the last dose/discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs):

SAR	Defined as all noxious and unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or are a congenital anomaly or birth defect.
SUSAR	A suspected SAR: refers to individual serious adverse event (SAE) case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the Sponsor or the investigator, is not listed is the applicable Reference Safety Information (RSI), and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. All individually reported SARs are considered suspected.

AbbVie will be responsible for SUSAR reporting for the investigational medicinal product (IMP) in accordance with global and local regulatory requirements in participating countries.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each adverse event according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. If a reported adverse event increases in severity, the initial adverse event should be given an end date and a new adverse event must be reported with a different onset date than the end date of the previous adverse event to reflect the change in severity. The dates of the adverse events cannot overlap.

For adverse events not captured by the NCI CTCAE, the following criteria should be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

For all reported serious adverse events that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "other" cause of the event.

The investigator will use the following definitions to assess the relationship of an adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

The investigator will assess the relationship of each adverse event to navitoclax and, if applicable, to ruxolitinib. For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated.

Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 30 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Toxicity Management

All subjects should be monitored according to the Activity Schedule in Appendix D for new-onset non-hematologic toxicity and renal toxicities, with dose delay or reduction as appropriate.

Navitoclax/Placebo

Navitoclax may be associated with cytopenias, notably thrombocytopenia, based on observations made of subjects during previous clinical trials in other indications and in the ongoing Study M16-109.

The guidelines noted below should be implemented for appropriate dosing and management of all subjects for safety. If additional dose reductions or modifications that are thought to be necessary by the investigator, a discussion with the AbbVie TA MD/SD is required.

- If a navitoclax/placebo interruption is necessary, navitoclax/placebo may be reintroduced at the same or lower dose based on the guidance below and in Table 1.
  - Current dose level 200 mg once daily; reduce to 100 mg once daily, then 50 mg once daily
  - Current dose; 100 mg once daily; reduce to 50 mg once daily.
- The same navitoclax/placebo dose level shall not be attempted more than twice consecutively without prior approval from the AbbVie TA MD/SD.
- Intermediate dose levels of navitoclax/placebo (e.g., 150 mg once daily) may be administered for moderate dose adjustments.

Ruxolitinib

For ruxolitinib, in addition to the dose modification guidelines provided below and in Table 1, the local, approved product label should be referenced for drug-drug interactions, precautions, monitoring, and dose adjustment guidelines for subjects with hepatic or renal impairment and all hematological and non-hematological toxicities.

For subjects who require interruption of ruxolitinib per the label but are considered to be at increased risk for exacerbation of splenomegaly and significant symptoms, ruxolitinib dose can be tapered by the Investigator in consultation with the AbbVie TA MD/SD followed by interruption.

Decisions regarding continued dosing, including the navitoclax/placebo or ruxolitinib dose level to be administered, for individual subjects will be medically managed by the investigator and consultation with the AbbVie TA MD/SD is recommended. Dosing interruptions greater than 28 days or additional dose modifications must be discussed with the AbbVie TA MD/SD.

Management of Thrombocytopenia and Bleeding Events

Navitoclax accelerates apoptosis of circulating mature platelets whether endogenous or transfused. This mechanism of toxicity differs from the thrombocytopenia caused by ruxolitinib and other conventional chemotherapy (i.e., toxicity to platelet progenitors in the bone marrow) and should, therefore, be managed according to the guidelines provided in Table 1, unless previously discussed and approved with the AbbVie TA MD/SD.

Hematology samples must be collected within 24 hours prior to the first dose of study drug to determine dose of study drug, at 4 hours after the first dose of study treatment, and on Day 2 (see Activity Schedule, Appendix D, and Operations Manual, Section 3.14). The investigator should consider additional hematology labs on Day 3 and/or Day 4 for subjects with a lower baseline platelet count and for subjects who experience a > 40% decrease in platelet count on Day 2 from the pre-dose platelet count. Additional hematology labs may be performed based on platelet counts as medically indicated at the investigator's discretion.

Any Grade ≥ 2 bleeding event (regardless of platelet count) will require interruption of dosing. Upon resolution of a Grade ≥ 2 bleeding event, study drug treatment may be reintroduced at the same or lower dose level (in consultation with the AbbVie TA MD/SD), provided the patient is asymptomatic with no evidence of an active bleeding.

If platelet transfusions are required in response to active bleeding, navitoclax/placebo dosing should be interrupted. It should be noted that platelet response with transfusions may not follow typical platelet kinetics of thrombocytopenia as with typical chemotherapy-induced thrombocytopenia. Procedures consistent with local institutional blood banking guidelines regarding platelet transfusions should be followed.

Platelet Transfusion Recommendations:

If platelet transfusion is deemed necessary, the treating physician should be aware that due to the rapid apoptotic effect of navitoclax on mature platelets, the increase in platelet counts post-transfusion may be lower and the duration of response may be shorter. Therefore, donor platelets collected as recently as possible prior to transfusion should be used. Additional transfusions may be necessary to achieve the desired platelet count. Post-transfusion platelet count monitoring should include:

- A platelet count obtained 10 to 60 minutes post transfusion.
- A platelet count obtained approximately 24 hours (± 1 hour) post transfusion.

Management of Neutropenia

There is a potential for clinically significant neutropenia given the toxicity profiles of both ruxolitinib and navitoclax. The management of neutropenia guidelines, as listed in Table 1 and below, should be implemented for all subjects unless previously discussed and approved with the AbbVie TA MD/SD.

- For Grade 3 neutropenia in addition to interruption as listed in Table 1, support with G-CSF and/or prophylaxis with antibiotics may be considered at the discretion of the investigator.
- For Grade 4 neutropenia in addition to interruption as listed in Table 1, support with G-CSF and/or prophylaxis with antibiotics may be considered at the discretion of the Investigator. If, in the opinion of the investigator, ruxolitinib dose can be resumed prior to recovery of ANC $\geq 1.0 \times 10^9$/L or needs a dose reduction, consultation with the AbbVie TA MD/SD is necessary.

At any time during the study, if the subject presents with febrile neutropenia, navitoclax/placebo and ruxolitinib, if applicable, should be interrupted until resolution of the fever or infection.

Table 1. Dose Adjustment Guidelines for Thrombocytopenia and Neutropenia

• **After navitoclax/placebo and/or ruxolitinib dose modification, platelet counts should be rechecked approximately 7 days or sooner as clinically applicable until at least 2 consecutive laboratory values indicate stable platelet count.** • **If treatment is interrupted for platelet count < 50 x 10^9/L, recheck platelets approximately every 2 to 3 days until recovery of platelets to ≥ 50 × 10^9/L.** • **Navitoclax/Placebo Dose levels for daily dosing: 200 mg, 150 mg, 100 mg, 75 mg, or 50 mg.**		
Hematology Results	**Navitoclax/Placebo**	**Ruxolitinib per approved local label**
Dose Modification for Thrombocytopenia		
Platelet counts ≥ 125 x 10^9/L	• Maintain dose if current navitoclax/placebo dose is 200 mg QD. • Increase dose by one dose level if current navitoclax/placebo dose is ≤ 150 mg QD and has been administered for at least 7 days without any dose modification or interruption.	• Increase dose to the label recommended dose for subjects who received lower starting dose of ruxolitinib than the label recommended dose if platelet counts are stable and current dose of ruxolitinib has been administered for at least 7 days without any dose modification or interruption.
Platelet counts ≥ 100 x 10^9/L to < 125 x 10^9/L	• Maintain dose if current navitoclax/placebo dose is ≥ 150 mg QD. • Increase dose by one dose level if current navitoclax/placebo dose is ≤ 100 mg QD and has been administered for at least 7 days without any dose modification or interruption.	• Maintain current ruxolitinib dose if receiving ≤ 15 mg twice daily. • Reduce dose to one dose level lower twice daily if current ruxolitinib dose ≥ 20 mg twice daily.
Platelet counts ≥ 75 × 10^9/L to < 100 × 10^9/L	• Maintain dose if current navitoclax/placebo dose is ≥ 150 mg QD. • Increase dose by one dose level if current navitoclax/placebo dose is ≤ 100 mg QD and has been administered for at least 7 days without any dose modification or interruption.	• Maintain current ruxolitinib dose if receiving ≤ 10 mg twice daily. • Reduce dose to 10 mg twice daily if current ruxolitinib dose ≥ 15 mg twice daily.

- **After navitoclax/placebo and/or ruxolitinib dose modification, platelet counts should be rechecked approximately 7 days or sooner as clinically applicable until at least 2 consecutive laboratory values indicate stable platelet count.**
- **If treatment is interrupted for platelet count < 50 x 10^9/L, recheck platelets approximately every 2 to 3 days until recovery of platelets to ≥ 50 × 10^9/L.**
- **Navitoclax/Placebo Dose levels for daily dosing: 200 mg, 150 mg, 100 mg, 75 mg, or 50 mg.**

Hematology Results	Navitoclax/Placebo	Ruxolitinib per approved local label
Platelet counts ≥ 50 × 10^9/L to < 75 × 10^9/L	• Reduce dose to one dose level lower. • Maintain dose if current navitoclax/placebo dose is 50 mg QD and counts are stable and no risk for bleeding per investigator discretion. • Interrupt dosing if current navitoclax/placebo dose is 50 mg QD and platelet counts are not stable and there is a risk for bleeding.	• Reduce dose to 5 mg twice daily.
Platelet counts < 50 × 10^9/L	• Interrupt dosing and resume at one dose level lower than prior to interruption once platelet counts recover to ≥ 50 × 10^9/L.	• Interrupt per local label. May taper if high risk for exacerbation in discussion with TA MD/SD. • Resume at same or lower dose once platelet counts recover ≥ 50 × 10^9/L.
Dose Modification for Neutropenia		
Absolute neutrophil count (ANC) < 1.0 × 10^9/L to 0.5 × 10^9/L	• Interrupt dosing and monitor hematology labs at least weekly until ANC ≥ 1.0 × 10^9/L. • Resume at one dose level lower than prior to interruption once ANC recover ≥ 1.0 × 10^9/ L.	• Maintain current dose or interrupt per local label if at risk for infection per investigator discretion.
Absolute neutrophil count (ANC) < 0.5 × 10^9/L	• Interrupt dosing and monitor hematology labs at least weekly or often as needed until ANC ≥ 1.0 × 10^9/L. • Resume at one dose level lower than prior to interruption once ANC recover ≥ 1.0 × 10^9/ L.	• Interrupt per local label. May taper if high risk for exacerbation in discussion with TA MD/SD. • Resume at same or lower dose.

Management of Infections

Subjects who develop clinically significant infections should have navitoclax/placebo and ruxolitinib interrupted and restart study drug treatment when signs or symptoms of infection have resolved.

If clinically indicated, anti-infective prophylaxis should be implemented at the investigator's discretion, including appropriate prophylaxis for viral, fungal, bacterial, or *Pneumocystis jiroveci* pneumonia infections with close monitoring as there is a potential for drug-drug interactions.

Management of Other Toxicities

For non-hematologic events, the investigator may interrupt and/or modify dosing of either of the study drugs, as clinically indicated. Consultation with AbbVie TA MD/SD prior to interruption or dose modification is recommended.

Grade ≥ 3 gastrointestinal toxicity of nausea, vomiting, and diarrhea when additional supportive care fails, increase in AST, ALT, and bilirubin (Grade determined from baseline value per CTCAE criteria) that might be attributed to navitoclax or ruxolitinib will require interruption and possible discontinuation of dosing if no improvement. Study drug treatment may be reintroduced at the same or lower dose level (in consultation with the AbbVie TA MD/SD) if the laboratory results or symptoms return to Grade ≤ 1 or to baseline at study entry.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The primary analysis will be performed after all ongoing, randomized subjects have completed at least 24 weeks of disease assessment or all subjects discontinue the study, whichever occurs first.

All statistical tests will be performed at two-sided significance level 0.05 unless otherwise specified.

7.2 Definition for Analysis Populations

The intent-to treat (ITT) population includes all randomized subjects in the study. Data from the ITT population will be analyzed by the treatment arm (Arm A: navitoclax + ruxolitinib, and Arm B: placebo + ruxolitinib) assigned at the time of randomization, regardless of the study drug treatment actually received. The ITT population will be used for analyses of all efficacy and baseline characteristics.

The safety population consists of all subjects who received at least 1 dose of study drug. The safety population will be used for all safety analyses.

7.3 Statistical Analyses for Efficacy

Primary Efficacy Analysis

Analysis of the primary endpoint SVR_{35W24} will be conducted by comparing the SVR_{35W24} rate (the proportion of subjects achieving SVR_{35} at Week 24), using the stratified Cochran-Mantel-Haenszel (CMH) test. The study is designed to test the null hypothesis:

H_0:SVR_{35W24} rate in Arm A (navitoclax + ruxolitinib) = SVR_{35W24} rate in Arm B (placebo + ruxolitinib) against the alternative hypothesis H_1:SVR_{35W24} rate in Arm A ≠ SVR_{35W24} rate in Arm B.

The stratification factors for the stratified statistical analyses will be described in detail in the SAP.

The 95% confidence interval (CI) for SVR_{35W24} rate will be estimated for each treatment arm based on the exact binomial distribution. Subjects without spleen volume assessment at baseline or the Week 24 timepoint will be treated as non-responders. Details of this analysis will be provided in the SAP.

Secondary Efficacy Analyses

The following secondary endpoints will be analyzed:

- Response rate endpoints: SVR_{35}, anemia response, reduction in grade of bone marrow fibrosis from baseline as measured by the European consensus grading system
- Continuous endpoints: Change in TSS at Week 24 from baseline, as measured by MFSAF v4.0; change in fatigue at Week 24 from baseline, as measured by the PROMIS Fatigue SF 7a; change in physical functioning at Week 24 from baseline, as measured by EORTC QLQ-C30 v3.0
- Time to event endpoints: Duration of SVR_{35}, OS, and LFS

Change in TSS at Week 24 from baseline is defined as the change in total symptom score at Week 24 from baseline, as measured by MFSAF v4.0.

SVR_{35} rate is defined as the proportion of subjects who achieve at least 35% reduction in spleen volume from baseline (SVR_{35}) at any time during the study.

Duration of SVR_{35} is defined as time from the first achievement of SVR_{35} to the first assessment where the spleen volume is less than 35% reduction from baseline and is at least 25% increase from the nadir (the lowest spleen volume).

Change in fatigue at Week 24 from baseline is defined as the change in fatigue score at Week 24 from baseline, measured by PROMIS Cancer Fatigue SF 7a.

Change in physical functioning at Week 24 from baseline is defined as the change in physical functioning score at Week 24 from baseline, as measured by EORTC QLQ-C30.

Anemia response rate is defined as the proportion of subjects who achieve anemia response at any time during the study.

Overall survival is defined as time from randomization to death from any cause.

Leukemia-free survival is defined as time from randomization to leukemic transformation (≥ 20% blasts) by bone marrow blasts or peripheral blood blasts per IWG criteria, or death from any cause, whichever occurs earlier.

Rate of reduction in grade of bone marrow fibrosis is defined as the proportion of subjects who achieve reduction of at least 1 grade in bone marrow fibrosis measured by the European consensus grading system.

Unless otherwise specified, all response rate secondary endpoints will be analyzed using the stratified CMH test. The point estimate and 95% CIs based on the exact binomial distribution will be presented for each treatment arm. Unless otherwise specified, subjects with missing data for a visit will be treated as non-responders for that visit.

Unless otherwise specified, all time to event secondary endpoints will be analyzed by using stratified log-rank test. Subjects who do not experience the event of interest will be censored at the last adequate assessment. The hazard ratio (HR) for treatment effect and the corresponding 95% CI will be estimated using stratified Cox proportional hazards model. In addition, survivorship functions will be estimated by using Kaplan-Meier product-limit method. Estimated survival curves will be presented.

Unless otherwise specified, all continuous patient-reported outcome endpoints will be analyzed using the linear mixed effects model. Subjects with missing data will be handled by the missing at random assumption within the framework of the linear mixed effects model.

Statistical analyses of secondary endpoints will be described in detail in the SAP.

Additional Efficacy Analyses

Details of additional efficacy analyses will be provided in the SAP. Additional supportive efficacy statistical analyses may be performed if deemed necessary and helpful in understanding the drug effect.

Subgroup Analysis for Efficacy

Supportive subgroup analyses, such as platelet count and DIPSS+, will be performed for the primary endpoint. Details of subgroup analyses will be provided in the SAP.

7.4 Statistical Analyses for Safety

Safety analyses will be performed using the safety population.

Details of the safety analyses will be provided in the SAP.

7.5 Interim Analysis

There is no plan for any interim efficacy analysis. However, an IDMC will review unblinded safety data from the ongoing study (see Section 5.12). The primary responsibility of the IDMC will be to protect the safety of the subjects participating in this study and make the necessary recommendations.

7.6 Overall Type I Error Control

Overall type I error rate will be controlled for multiplicity for the primary and selected secondary efficacy endpoints. Hierarchical/sequential testing approach will be used to control the overall type I error rate at two-sided 0.05 significance level.

The key secondary efficacy endpoints are ranked as follows: 1. Change in TSS at Week 24 from baseline; 2. SVR_{35}; 3. Anemia response; 4. Reduction in grade of bone marrow fibrosis from baseline; 5. OS; 6. LFS; 7. Change in fatigue at Week 24 from baseline; 8. Change in physical functioning at Week 24 from baseline.

For endpoints to be analyzed more than once (such as OS and LFS), the Lan-DeMets alpha-spending function with O'Brien-Fleming boundary will be used to determine the efficacy boundaries for planned analyses. Additional details will be provided in SAP.

7.7 Sample Size Determination

Approximately 230 subjects will be enrolled using a 1:1 randomization ratio to Arm A and Arm B by the stratification factors (DIPSS+: intermediate-2 versus high risk, and platelet count: $\leq 200 \times 10^9$/L versus $> 200 \times 10^9$/L). The null hypothesis H_0 will be tested against the alternative hypothesis H_1 using the stratified CMH test with two-sided significance level 0.05.

Based on published results, the SVR_{35W24} rate in the control arm (Arm B) is expected to be approximately 40%.[15] True improvement in SVR_{35W24} from 40% to [redacted] is considered clinically meaningful.

This study with 230 subjects will have approximately 90% power if the true SVR_{35W24} rates in the control (placebo + ruxolitinib) and treatment (navitoclax + ruxolitinib) arms are 40% and [redacted], respectively.

With a total of 230 subjects, the study will also have approximately [redacted] power to detect a statistically significant OS improvement in the navitoclax + ruxolitinib treatment arm, assuming a true hazard ratio of [redacted]. A total of two OS analyses are planned: the first will be performed at the time of approximately 70% OS information (or [redacted] death events); the final OS Analysis will be performed when a total of [redacted] death events (100% OS information) have been observed. The Lan-DeMets alpha-spending function with O'Brien-Fleming boundary will be used to determine the efficacy boundaries for these planned OS analyses.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will

require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s) including the archiving of essential documents. During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data

will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of the last subject's last visit or date of last follow-up contact with the subject, whichever is later, in the last country where the study was conducted.

12 REFERENCES

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
Ag	antigen
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{0-12}	Area under the curve from 0 to 12 hours
BCL-2	B-cell lymphoma-2
BCRP	Breast cancer resistance protein
BET	Bromodomain and extra-terminal motif
BH3	B-cell lymphoma 2 homology 3
BUN	Blood urea nitrogen
CI	Confidence interval
CL/F	Apparent oral clearance
CLL	Chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CSF	Colony stimulating factor
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DIPSS+	Dynamic International Prognostic Scoring System Plus
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
DTP	Direct-to-patient
EC_{50}	Concentration required for 50% effect
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessments
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

EDC	Electronic data capture
ELN	European LeukemiaNet
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Health State Instrument
ESR	Erythrocyte sedimentation rate
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence In Situ Hybridization
FLT3	FMS-like tyrosine kinase 3
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
Hb	Hemoglobin
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMR	High molecular risk
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IGRA	Interferon-gamma release assay
IMP	Investigational medicinal product
INR	International normalized ratio
Int	Intermediate
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWG	International Working Group

JAK1	Janus kinase 1
JAK2	Janus kinase 2
LDL	Low-density lipoprotein
LFS	leukemia-free survival
LMWH	Low molecular weight heparin
MCL-1	Myeloid cell leukemia 1
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MRI	Magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCI	National Cancer Institute
NRS	Numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCP	Pneumocystis carinii pneumonia
PET	Post essential thrombocythemia
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
P-gp	P-glycoprotein
PK	Pharmacokinetic
Plt	Platelet
PMF	Primary myelofibrosis
PPD	Purified protein derivative
PPV	Post polycythemia vera
PR	Partial remission
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Prothrombin time
Q12	Every 12 (weeks)
Q24	Every 24 (weeks)
QLQ	Quality of life questionnaire

QoL	Quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
RNA	Ribonucleic acid
RPTD	Recommended Phase 2 dose
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDAC	Statistical data analysis center
SF	Short form
SMF	Secondary myelofibrosis
SmPC	Summary of product characteristics
SOC	System organ class
SSRI	Selective serotonin re-uptake inhibitors
SUSAR	Suspected unexpected serious adverse reaction
SVR_{35}	At least 35% spleen volume reduction from baseline
SVR_{35W24}	At least 35% reduction in spleen volume at Week 24 from baseline
TA MD/SD	Therapeutic Area Medical Director/Scientific Director
TB	Tuberculosis
TCV	Treatment completion visit
TSS	Total symptom score
TSS_{50W24}	At least 50% reduction in total symptom score at Week 24 from baseline
ULN	Upper limit of normal
USA	United States of America
USPI	United States prescribing information
v	Version
VAS	Visual analogue scale
V/F	Apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-191: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Navitoclax in Combination with Ruxolitinib Versus Ruxolitinib in Subjects with Myelofibrosis (TRANSFORM-1)

Protocol Date: 23 March 2023

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Study Leadership
		Clinical Study Leadership
		TA Oncology
		Statistics
		Health Economics & Outcomes Research
		Patient Experience Data & Strategy
		Clinical Development Oncology
		Medical Writing

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities. The individual activities are described in detail in the **Operations Manual**.

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Study Activities Table

Activity	Screening/ Baseline Day –28 to Day –1	Week 1 Day 1	Week 1 Day 2	Week 2 Day 1 (± 1 day)	Week 3 Day 1 (± 1 day)	Week 5 Day 1 (± 1 day)	Week 7 Day 1 (± 1 day).	Week 9 Day 1 (± 1 day)	Week 13, 17, 21, 25 Week 13, 17, 21 Day 1 (± 2 days). Week 25 Day 1 (± 3 days)	Q12 weeks as of Week 37 From Week 37 Day 1 (± 4 days)	Treatment Completion Visit	30-Day Safety Visit (± 3 Days)	Post-Treatment Visits (± 3 Weeks)	Survival Follow Up
INTERVIEWS & QUESTIONNAIRES														
Informed consent	✓													
Eligibility criteria	✓													
Medical/surgical/transfusion history	✓	✓												
Alcohol and nicotine use	✓													
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Prior/concomitant therapy/transfusion	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Post-treatment therapy/transfusion/surgery												✓	✓	✓
MFSAF v4.0 (Daily)	✓	✓(Daily through end of Week 36)												
EORTC QLQ-C30 v3.0		✓				✓			✓ (Week 13, 25)	✓	✓			
PROMIS Fatigue SF 7a	✓	✓				✓			✓ (Week 13, 25)	✓	✓			
EQ-5D-5L		✓				✓			✓ (Week 13, 25)	✓	✓			
PGIC									✓ (Week 13, 25)					

Activity	Screening/ Baseline Day –28 to Day –1	Week 1 Day 1	Week 1 Day 2	Week 2 Day 1 (± 1 day)	Week 3 Day 1 (± 1 day)	Week 5 Day 1 (± 1 day)	Week 7 Day 1 (± 1 day).	Week 9 Day 1 (± 1 day)	Week 13, 17, 21, 25 Week 13, 17, 21 Day 1 (± 2 days). Week 25 Day 1 (± 3 days)	Q12 weeks as of Week 37 From Week 37 Day 1 (± 4 days)	Treatment Completion Visit	30-Day Safety Visit (± 3 Days)	Post-Treatment Visits (± 3 Weeks)	Survival Follow Up
PGIS	✓	✓							✓ (Week 13, 25)					
ECOG performance status	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓			
Survival follow-up call (approximately every 2 months for up to 8 years)														✓
LOCAL LABS & EXAMS														
MRI (or CT scan) for spleen assessment	✓								✓ (Week 13, 25)	✓ (Week 37, 49, 73, 97)	✓		✓	
12-lead ECG	✓					✓					✓			
Vital signs: including height (Screening only), weight, BP, pulse, and body temperature	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		
Physical examination including skin examination, spleen and liver measurement by palpation	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	
Disease Assessment by IWG									✓ (Week 13, 25)	✓ (Week 37, 49, 73, 97)	✓		✓	
Serum/urine pregnancy test	✓	✓				✓		✓	✓ (monthly from Week 25 where a	✓ (monthly where a regulatory requirement)	✓			

Activity	Screening/ Baseline Day –28 to Day –1	Week 1 Day 1	Week 1 Day 2	Week 2 Day 1 (± 1 day)	Week 3 Day 1 (± 1 day)	Week 5 Day 1 (± 1 day)	Week 7 Day 1 (± 1 day).	Week 9 Day 1 (± 1 day)	Week 13, 17, 21, 25 Week 13, 17, 21 Day 1 (± 2 days). Week 25 Day 1 (± 3 days)	Q12 weeks as of Week 37 From Week 37 Day 1 (± 4 days)	Treatment Completion Visit	30-Day Safety Visit (± 3 Days)	Post-Treatment Visits (± 3 Weeks)	Survival Follow Up
									regulatory requirement)					
TB screening (PPD or IGRA)	✓													
Clinical chemistry, hematology, coagulation	✓	✓	✓ (hem only)	✓	✓	✓	✓	✓	✓	✓	✓		✓ (hem only)	
Lipid parameters – fasting state	✓								✓ (Week 13)					
Bone marrow biopsy and cytogenetic assessment (Screening plus standard of care) for local evaluation of disease	✓								✓ (Week 25)	✓ (Week 49, 73)	✓		✓	
Bone marrow aspirate for local evaluation of disease	✓								✓ (Week 25)	✓ (Week 49, 73)	✓		✓	
CENTRAL LAB														
Blood samples for PK assay		✓		✓	✓	✓								
Blood for mutational profiling	✓								✓ (Week 13, 25)	✓ (Week 49, 73)	✓			
Blood for immune cell biology		✓							✓ (Week 25)	✓ (Week 49)				
Blood for PBMC		✓							✓ (Week 25)	✓ (Week 49)				

Activity	Screening/ Baseline	Week 1	Week 1	Week 2	Week 3	Week 5	Week 7	Week 9	Week 13, 17, 21, 25	Q12 weeks as of Week 37	Treatment Completion Visit	30-Day Safety Visit (± 3 Days)	Post-Treatment Visits (± 3 Weeks)	Survival Follow Up
	Day –28 to Day –1	Day 1	Day 2	Day 1 (± 1 day)	Day 1 (± 1 day)	Day 1 (± 1 day)	Day 1 (± 1 day).	Day 1 (± 1 day)	Week 13, 17, 21 Day 1 (± 2 days). Week 25 Day 1 (± 3 days)	From Week 37 Day 1 (± 4 days)				
Blood for plasma markers	✓								✓ (Week 13, 25)	✓ (Week 49)	✓			
Blood for allelic burden	✓								✓ (Week 13, 25)	✓ (Week 49, 73)	✓			
Blood for translational research	✓								✓ (Week 13, 25)	✓ (Week 49, 73)	✓			
Bone marrow biopsy (fibrosis grading/biomarker research)	✓								✓ (Week 25)	✓ (Week 49, 73)	✓		✓	
Bone marrow aspirate for mutational profiling	✓								✓ (Week 25)	✓ (Week 49, 73)	✓			
Bone marrow aspirate for allelic burden	✓								✓ (Week 25)	✓ (Week 49, 73)	✓			
Bone marrow aspirate for translational research	✓								✓ (Week 25)	✓ (Week 49, 73)	✓			
Optional Biomarker Sample: Whole Blood DNA and RNA		✓							✓ (Week 13)		✓			

Activity	Screening/ Baseline Day –28 to Day –1	Week 1 Day 1	Week 1 Day 2	Week 2 Day 1 (± 1 day)	Week 3 Day 1 (± 1 day)	Week 5 Day 1 (± 1 day)	Week 7 Day 1 (± 1 day).	Week 9 Day 1 (± 1 day)	Week 13, 17, 21, 25 Week 13, 17, 21 Day 1 (± 2 days). Week 25 Day 1 (± 3 days)	Q12 weeks as of Week 37 From Week 37 Day 1 (± 4 days)	Treatment Completion Visit	30-Day Safety Visit (± 3 Days)	Post-Treatment Visits (± 3 Weeks)	Survival Follow Up
℞ TREATMENT														
Randomization/drug assignment		✓												
Dispense study drug; dispense subject dosing diary (Week 1 Day 1)		✓		✓	✓	✓	✓	✓	✓	✓				
Review and copy subject dosing diary (Week 1 Day 1 to Week 5 Day 1) and perform drug reconciliation				✓	✓	✓	✓	✓	✓	✓	✓			

APPENDIX E. WORLD HEALTH ORGANIZATION DIAGNOSTIC CRITERIA FOR PRIMARY MYELOFIBROSIS

	Primary Myelofibrosis (PMF) – Overt PMF
Major Criteria	1. Megakaryocyte proliferation and atypia[a] accompanied by either reticulin and/or collagen fibrosis (Grade 2 or 3). 2. Not meeting WHO criteria for *BCR-ABLI* + CML, PV, ET, MDS, or other myeloid neoplasm. 3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence, the presence of another clonal marker[b] or absence of evidence for reactive BM fibrosis.[c]
Minor Criteria	Presence of one or more of the following confirmed in two consecutive determinations: • Anemia not attributed to a comorbid condition • Leukocytosis ≥ 11 × 10^9/L • Palpable splenomegaly • LDH levels above the upper limit of the institutional reference range • Leukoerythroblastosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5807384/

a. Small-to-large megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.

b. In the absence of any of the three major clonal mutations, the search for the most frequent accompanying mutations *(ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1*) are of help in determining the clonal nature of the disease.

c. BM fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia, or other lymphoid neoplasm, metastatic malignancy or toxic (chronic) myelopathies.

APPENDIX F. DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS) AND DIPSS PLUS (DIPSS+) FOR SURVIVAL IN PRIMARY MYELOFIBROSIS

DIPSS[16]

Progonostic Variable	Points		
	0	1	2
Age, y	≤65	>65	
White blood cell count, x10^9/L	≤25	>25	
Hemoglobin, g/dL	≥10		<10
Peripheral blood blast, %	<1	≥1	
Constitutional symptoms, Y/N	N	Y	

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1 or 2
Intermediate-2 (INT-2)	3 or 4
High	5 or 6

DIPSS+[16]

Prognostic Variable	Points
DIPSS low-risk	0
DIPSS intermediate-risk 1 (INT-1)	1
DIPSS intermediate-risk 2 (INT-2)	2
DIPSS high-risk	3
Platelets <100 x 10^9/L	1
Transfusion need	1
Unfavorable karyotype*	1

*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q-, i(17q), 5/5q-, 12p-, inv(3), or 11q23 rearrangement.

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1
Intermediate-2 (INT-2)	2 or 3
High	4 to 6

APPENDIX G. SAMPLE LIST OF EXCLUDED AND CAUTIONARY MEDICATIONS

Prohibited Medications	
Anticoagulation Therapy (Excluded) warfarin (Coumadin) and coumarin derivatives e.g., phenprocoumon fondaparinux (Arixtra) heparin[a] melagatran/ximelagatran rivaroxaban (Xarelto) apixaban (Eliquis)	**Antiplatelet (Excluded)** acetylsalicylic acid (aspirin) > 100 mg once daily aspirin/extended release dipyridamole (Aggrenox) clopidogrel (Plavix) dipyridamole (Persantine) ticlopidine (Ticlid) tirofiban (Aggrastat)
Potential prolongation of prothrombin time (PT) (Excluded) disulfiram	
Cautionary Medications	
Strong CYP3A Inhibitors (Cautionary)[b] boceprevir clarithromycin cobicistat conivaptan danoprevir/ritonavir elvitegravir/ritonavir idelalisib indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil nefazodone nelfinavir paritaprevir/ritonavir Posaconazole ritonavir saquinavir telaprevir telithromycin tipranavir/ritonavir troleandomycin voriconazole	**Strong CYP3A Inducers (Cautionary)[b]** apalutamide avasimibe carbamazepine enzalutamine mitotane phenytoin rifampin St John's wort

CYP2C8 Substrates (Cautionary)[b,c]	**CYP2C9 Substrates (Cautionary)[b]**
amiodarone amodiaquine cerivastatin chloroquine lovastatin[d] paclitaxel (Taxol) pioglitazone repaglinide rosiglitazone simvastatin (Zocor)[d] troglitazone	fluvastin glipizide irbesartan losartan phenytoin sulfamethoxazole sulfinpyrazone tolbutamide torsemide
P-gp Substrates (Cautionary)[b]	**BCRP Substrates (Cautionary)[b]**
dabigatran etexilate digoxin fexofenadine	rosuvastatin sulfasalazine
P-gp Inhibitors (Cautionary)[b]	**BCRP Inhibitors (Cautionary)[b]**
amiodarone carvedilol clarithromycin dronedarone itraconazole lapatinib lopinavir and ritonavir propafenone quinidine ranolazine ritonavir saquinavir telaprevir tipranavir ritonavir verapamil	curcumin cyclosporine A eltrombopag
P-gp Inducers (Cautionary)[e]	**BCRP Inducers (Cautionary)[f]**
rifampin phenytoin carbamazepine St John's wort quercetin curcumin	efavirenz rifampin phenytoin quercetin curcumin omeprazole imatinib

Anticoagulation Therapy (Cautionary)	**SSRIs and SNRIs (Cautionary)**
low molecular weight heparin dalteparin (Fragmin) enoxaparin (Lovenox) tinzaparin (Innohep)	citalopram (Celexa) escitalopram (Lexapro) fluoxetine (Prozac) paroxetine (Paxil) sertraline (Zoloft) duloxetine (Cymbalta) vortioxetine (Trintellix) venlafaxine (Effexor) Desvenlafaxine (Pristiq)
NSAIDS[g] (Cautionary) Aspirin > 100 mg daily Celecoxib Diclofenac Diflunisal Etodolac Ibuprofen Indomethacin Ketoprofen Nabumetone Naproxen Oxaprozin Salsalate Sulindac Tolmetin	

CYP = cytochrome P450; P-gp = P-glycoprotein; SSRI = Selective serotonin re-uptake inhibitors

a. Heparin may be used for patency of a central venous catheter and temporary use for prophylaxis of deep vein thrombosis.

b. This is not an exhaustive list. For an updated list, see the following link http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

c. Only certain statins qualify as CYP2C8 substrates.

d. Significant increase in area under the curve (AUC) by co-administration of gemfibrozile, a potent CYP2C8 inhibitor. However, the involvement of CYP2C8 is unclear.

e. This is not an exhaustive list. Elmeliegy M et al, Clinical Pharmacokinetics (2020);59:699-714.

f. This is not an exhaustive list. Gameiro M et al, Molecules (2017);22(4):600.

g. Certain NSAIDS are also CYP2C9 substrates. NSAIDS are allowed for limited use only if platelets >100 x 10^9/L.

APPENDIX H. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	28 February 2020
Version 2.0	24 June 2020
Version 2.1 (France Only)	01 September 2020
Version 2.2 (Sweden Only)	09 September 2020
Version 2.3 (United Kingdom Only)	10 September 2020
Version 2.4 (Belgium Only)	23 September 2020
Version 2.4.1 (Belgium Only)	13 October 2020
Version 3.0	05 November 2020
Version 4.0	27 May 2021
Administrative Change 1	24 November 2021
Version 5.0	03 February 2022
Version 6.0	31 March 2022
Administrative Change 2 (Japan Only)	12 July 2022

The purpose of this version is to correct minor clerical/typographical errors for consistency throughout the protocol and the following:

- Updated Protocol Section 3.2 to clarify the second efficacy endpoints of the change in TSS and change in physical functioning. Overall response of clinical improvement was also removed as a secondary efficacy endpoint.
- Updated Protocol Section 3.3 to include additional exploratory endpoints.
- Updated Protocol Section 5.5 to include additional information about continuation of study treatment for subjects with disease progression or relapse.
- Updated Protocol Section 5.5 to clarify guidance on study drug interruption in case of COVID-19 confirmation/suspicion during study treatment period.
- Updated Protocol Section 6.2 to correct typo error in Table 1. for ruxolitinib dose adjustment guidelines.
- Updated Protocol Section 7.3 to clarify that stratification factors for stratified analyses in the primary efficacy analysis can be found in the SAP.
- Updated Protocol Section 7.3 to define changes in TSS and physical functioning for secondary efficacy analysis. Additionally, it was clarified that a linear mixed effects model will be used for all continuous patient-reported outcome endpoints unless otherwise specified.

- Updated Protocol Section 7.6 to reflect changes in secondary efficacy endpoints and their rankings.
- Updated Protocol Section 7.7 to include information on planned OS analyses.
- Added Section 5.5 in the Operations Manual in order to identify "Drugs used in the Clinical Trial" in accordance with revisions to local guidance in Japan.