1.0 Title Page

Clinical Study Protocol M16-109

A Phase 2 Open-Label Study Evaluating Tolerability and Efficacy of Navitoclax Alone or in Combination with Ruxolitinib in Subjects with Myelofibrosis (REFINE)

Incorporating Administrative Changes 1 and 2 (United States and Puerto Rico Only) and Amendments 1, 2, 3, 4, 5, 6, 7, 8, 8.01 (Spain and Italy Only), 9, 10, and 11

AbbVie Investigational Product:	Navitoclax (ABT-263)
Date:	04 October 2021
Development Phase:	2
Study Design:	This is a Phase 2 open label, multicenter study evaluating tolerability and efficacy of navitoclax alone or in combination with ruxolitinib in subjects with myelofibrosis.
EudraCT Number:	2017-001398-17
Investigator:	Investigator information on file at AbbVie.
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This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	07 April 2017
Protocol Amendment 1	30 June 2017
Protocol Amendment 2	27 July 2017
Protocol Amendment 3	20 February 2018
Protocol Amendment 4	31 March 2018
Administrative Change 1	04 May 2018
Protocol Amendment 5	10 September 2018
Protocol Amendment 6	13 August 2019
Protocol Amendment 7	06 December 2019
Protocol Amendment 8	04 June 2020
Administrative Change 2 (US, PR only)	23 September 2020
Protocol Amendment 8.01 (ES, IT only)	24 September 2020
Protocol Amendment 9	22 October 2020
Protocol Amendment 10	23 June 2021

The purpose of this amendment is to:

- Revise Section 1.2, Synopsis, Key Exclusion

  Rationale: *Clarified that moderate CYP3A inhibitors (e.g., fluconazole) are prohibited for Cohort 1b DDI sub-study subjects.*
- Revise Section 5.2.2, Exclusion Criteria, Rationale for Exclusion Criteria

  Rationale: *Corrected that exclusion criteria 13 is due to unknown impact of navitoclax on sperm count, the unborn fetus or breastfeeding infant.*
- Revise Section 5.2.4, Prior and Concomitant Therapy

  Rationale: *Clarified that moderate CYP3A4 inhibitors (e.g., fluconazole) should be used with caution for subjects receiving ruxolitinib.*

- Revise Section 5.2.5 Contraception Recommendations

  Rationale:

  Removed reference to premenarchal females as subjects must be age 18 or older.

  Removed "progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action and barrier methods listed as they were included in error with Protocol Amendment 10 and are not considered highly effective methods of birth control.

  Added that if required per local practice, protocol-required birth control methods (excluding true abstinence) should be supplemented with barrier methods such as male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide.

- Revise Section 5.3.1.1, Study Procedures, Pregnancy Testing

  Rationale: *Clarified that negative pregnancy test prior to dosing on Study Day 1 may be determined via urine or serum.*

- Revise Section 5.3.1.1, Study Procedures, Clinical Laboratory Tests

  Rationale: *Corrected footnote reference for Creatinine Clearance to e, which states that it is required at screening but can be performed at investigators discretion during the study.*

- Update Appendix G Dynamic International Prognostic Scoring System (DIPSS)

  Rationale: *Footnote * added to Table 14 to specify that in order to report constitutional symptoms as yes for DIPSS scoring, at least one of the following symptoms must be present: weight loss, fever, or night sweats.*

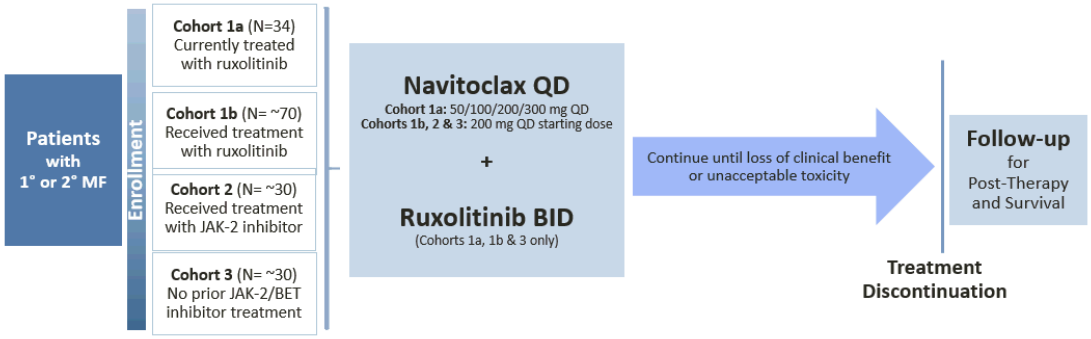
- Correct typographical errors and minor language or word revisions throughout the document. Update AbbVie contact information throughout the protocol.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-109
Name of Study Drug: Navitoclax (ABT-263)	**Phase of Development:** Phase 2
Name of Active Ingredient: Navitoclax (ABT-263)	**Date of Protocol Synopsis:** 04 October 2021
Protocol Title: A Phase 2 Open-Label Study Evaluating Tolerability and Efficacy of Navitoclax Alone or in Combination with Ruxolitinib in Subjects with Myelofibrosis (REFINE)	
Objective(s): The primary objective of the study is: • To evaluate the effect of navitoclax alone or in combination with ruxolitinib on spleen volume The secondary objectives of the study are: • To assess the effect of navitoclax alone or in combination with ruxolitinib on total symptom score (TSS) as assessed by the Myelofibrosis Symptom Assessment Form (MFSAF) version 4.0 diary • To evaluate the effect of navitoclax alone or in combination with ruxolitinib on bone marrow fibrosis • To determine the rate of anemia response associated with navitoclax alone or in combination with ruxolitinib • To describe the safety profile and PK profile observed with navitoclax alone or in combination with ruxolitinib Exploratory objectives of the study include, but is not limited to the evaluation of the duration of disease response including effects on spleen and anemia, survival, impact on quality of life and translational biomarkers.	
Investigator(s): Multi-center	
Study Site(s): Approximately 135 sites	
Study Population: Subjects with primary or secondary (post-polycythemia vera MF [PPV-MF]), post-essential thrombocythemia [PET-MF]) myelofibrosis who have received prior treatment with ruxolitinib (Cohorts 1a and 1b,) or any JAK-2 inhibitor (Cohort 2) OR who have not received prior treatment with a JAK2 inhibitor or BET inhibitor (Cohort 3).	
Number of Subjects to be Enrolled: Approximately 174 subjects	

Methodology:

Figure 1. Study Schema



This Phase 2, multicenter, open-label study (Figure 1) evaluates the tolerability and efficacy of navitoclax alone or in combination with ruxolitinib in subjects with primary or secondary myelofibrosis. For Cohort 1a, subjects must have received ruxolitinib therapy for at least 12 weeks and currently be on a stable dose of ≥ 10 mg twice daily of ruxolitinib. For Cohorts 1b subjects must have received treatment with ruxolitinib. Cohort 1b will enroll approximately 80 subjects to ensure enrollment of approximately 70 subjects with prior exposure to ruxolitinib. For Cohort 2, subjects must have received prior treatment with a JAK-2 inhibitor. For Cohort 3, subjects must not have received prior treatment with a JAK-2 inhibitor or BET inhibitor. Navitoclax will be administered at a starting dose of 50 mg once daily (Cohort 1a) or at 100 or 200 mg once daily (Cohorts 1b, 2 and 3).

Cohort 1a

The dose of navitoclax may be increased after approximately 7 or more days to the next dose level provided the platelet count is ≥ 75 × 10^9/L up to a maximum dose of navitoclax 300 mg once daily.

Cohorts 1b, 2 or 3

- Baseline Platelet Count >150 × 10^9/L: 200mg once daily navitoclax starting dose
- Baseline platelet count ≤ 150 × 10^9/L: 100mg once daily navitoclax starting dose
  - The dose of navitoclax may be increased to 200 mg once daily after 7 days provided the platelet count is ≥ 75 × 10^9/L
- The dose of navitoclax should not exceed 200 mg once daily for the first 24 weeks of treatment. After the Week 24 disease assessment, the dose of navitoclax may be increased to 300 mg once daily at the discretion of the Investigator for subjects with sub-optimal spleen response defined as failure to achieve spleen volume reduction of at least 10% as assessed by imaging.

Subjects in Cohorts 1a, 1b and 3 will receive ruxolitinib administered orally twice daily (BID). Subjects in Cohort 1a and 1b receiving ruxolitinib at screening will continue at the current stable dose of ≥ 10 mg twice daily. Subjects in Cohorts 1b not receiving ruxolitinib at the time of screening will receive ruxolitinib at a dose of 10 mg twice daily beginning on Day 1.

Subjects in Cohort 3 will receive ruxolitinib at the individualized starting dose based on baseline platelet count as per the local approved ruxolitinib label.

Subjects in Cohort 2 will receive Navitoclax monotherapy.

Laboratory Visits and Evaluation Schedule

Laboratory visits:

- Hematology and Chemistry: Screening, Pre-dose on Day 1, Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 and q12 weeks thereafter
- Hematology: 4 hours after the first dose of navitoclax on Day 1, 24 hours post-first-dose on Day 2, and prior to navitoclax dose increases, reductions, or re-initiation after interruption.

Clinic/Efficacy Evaluation visits:

- Clinic Assessments (including spleen and liver palpation): Screening, Day 1, Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 and q12 weeks thereafter
- MFSAF version 4.0 diary: Daily beginning at the Screening Visit, including pre-dose on Day 1 through the Week 36 Visit. For subjects enrolled in Cohorts 1b and 3 the screening period should be long enough to ensure at least 7 days to collect the daily MFSAF version 4.0 prior to Day 1
- EORTC QLQ-C30 QOL questionnaire: Screening, pre-dose on Day 1, Weeks 4, 8, 12, 24, every 12 weeks thereafter and at the TCV
- PROMIS Fatigue SF 7a questionnaire: Screening, pre-dose on Day 1, Weeks 4, 8, 12, 24, every 12 weeks thereafter and at the TCV
- PGIC questionnaire: pre-dose on Weeks 4, 8, 12, 24, every 12 weeks thereafter and at the TCV
- Imaging for spleen assessment: Screening, Weeks 12, 24, 36, 48, 72 and 96. After 96 weeks of treatment, an MRI/CT should be performed if disease progression is suspected.
- Bone marrow biopsy and aspirate: Screening, Weeks 12, 24, 48 and 96. After 96 weeks of treatment, bone marrow sampling should be performed if disease progression is suspected.
- Disease Assessment based on modified IWG: will be performed at Week 12, 24, 36, 48, 72 and 96. Disease assessment should also occur at any other time if disease progression is suspected or when imaging/bone marrow sampling is performed.

Pharmacokinetic samples will be collected and analyzed throughout the study. Additional samples will be collected for approximately 10 subjects in Cohort 1b who agree to provide blood samples to assess drug-drug interactions between navitoclax and ruxolitinib.

Exploratory biomarker specimens will be collected throughout the study. Analyses may include, but are not limited to allelic burden, mutational status, cytokines, and/or characterization of Bcl-2 and associated proteins.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Key Inclusion:

- Subjects ≥ 18 years of age
- Subjects with documented diagnosis of Primary MF, PPV-MF or PETMF as defined by the World Health Organization classification
- Subjects classified as intermediate-2 or high-risk MF, as defined by the Dynamic International Prognostic Scoring System (DIPSS)
- Subject must be ineligible due to age, comorbidities, or unfit for unrelated or unmatched donor transplantation or unwilling to undergo stem cell transplantation at time of study entry
- ECOG 0, 1, or 2

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Key Inclusion (Continued):

- **Cohort 1a only:** Subject must have received ruxolitinib therapy for at least 12 weeks and be currently on a stable dose of ≥ 10 mg twice daily of ruxolitinib for ≥ 8 weeks prior to the 1st dose of navitoclax.

  Note: Subjects with ruxolitinib dose reductions within 8 weeks prior to study enrollment may be considered on a stable dose if stable at that decreased dose of ruxolitinib for ≥ 2 weeks prior to the 1st dose of navitoclax. If the dose reduction was due to thrombocytopenia, the platelets must be confirmed to be stable by a repeat laboratory test.
- **Cohort 1b only:** Subject must have received treatment with ruxolitinib and meet at least one of the following criteria:
  - Prior or current treatment with ruxolitinib for ≥ 24 weeks with lack of efficacy defined as a lack of spleen response (refractory) or a loss of spleen or symptom response (relapsed)
  - Prior or current treatment with ruxolitinib for < 24 weeks with documented disease progression while on ruxolitinib as defined by any of the following:
    - Appearance of new splenomegaly that is palpable to at least 5 cm below the left costal margin (LCM) in subjects with no evidence of splenomegaly prior to the initiation of ruxolitinib.
    - A ≥ 100% increase in the palpable distance below the LCM in subjects with measurable spleen distance 5 to 10 cm prior to the initiation of ruxolitinib.
    - A ≥ 50% increase in the palpable distance below the LCM in subjects with measurable spleen distance > 10 cm prior to the initiation of ruxolitinib.
    - A spleen volume increase of ≥ 25% (as assessed by MRI or CT scan) in subjects with a spleen volume assessment prior to the initiation of ruxolitinib.
  - Prior or current treatment with ruxolitinib for ≥ 28 days with intolerance defined as new RBC transfusion requirement (at least 2 units/month for 2 months), while receiving a total daily ruxolitinib dose of ≥ 30 mg but unable to reduce dose further due to lack of efficacy.
- **Cohort 1b only:** Subjects that are receiving ruxolitinib at the time of screening, must currently be on a stable dose ≥ 10 mg twice daily of ruxolitinib for ≥ 4 weeks prior to the 1st dose of navitoclax.

  Note: Subjects with ruxolitinib dose reductions within 4 weeks prior to study enrollment are considered to be on a stable dose if dose of ruxolitinib if the dose is unchanged for ≥ 2 weeks prior to Day 1of navitoclax. The current dose must be ≥ 10 mg twice daily. If the dose reduction was due to thrombocytopenia, platelet counts must be confirmed to be stable by a repeat laboratory test.
- **Cohort 1b only:** Subject must not have received treatment with a BET inhibitor or an alternate JAK-2 inhibitor other than ruxolitinib.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Key Inclusion (Continued):

- **Cohort 2 only:** Subject must have received prior treatment with JAK-2 inhibitor therapy and meet one of the following criteria (a or b):
  a. Prior treatment with JAK-2 inhibitor for at least 12 weeks
  b. Prior treatment with JAK-2 inhibitor for ≥ 28 days complicated by any of the following:
     i. Development of red blood cell transfusion requirement (at least 2 units/month for 2 months)

     OR

     ii. Grade ≥ 3 adverse events of thrombocytopenia, anemia, hematoma and/or hemorrhage while on JAK-2 inhibitor treatment
- **Cohort 3 only:** Subject must not have received prior treatment with a JAK-2 or BET inhibitor
- Subject has splenomegaly defined as spleen palpation measurement ≥ 5 cm below costal margin or spleen volume ≥ 450 cm^3 as assessed by MRI/CT
- **Cohorts 1b and 3 only:** Subject has at least 2 symptoms each with a score ≥ 3 or a total score of ≥ 12, as measured by the MFSAF v4.0, on at least 4 out of 7 days during screening, prior to study drug dosing.
- Subject must meet the following laboratory parameters per local laboratory reference range during screening, prior to study drug dosing:
  - Adequate bone marrow reserves; in the absence of growth factors, thrombopoietic factors, or platelet transfusions for at least 14 days:
    - Platelet count ≥ 100×10^9/L (Cohorts 1a, 1b or 3)
    - Platelet count ≥ 75×10^9/L (Cohort 2)
    - ANC ≥ 1×10^9/L
  - Renal function: calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault formula
  - Hepatic function and enzymes:
    - AST and ALT ≤ 3.0 × the upper normal limit (ULN)
    - Total Bilirubin ≤ 1.5 × ULN (exception: subjects with Gilbert's Syndrome may have a Bilirubin > 1.5 × ULN)
  - Coagulation: aPTT and prothrombin time (PT) or INR ≤ 1.5 × ULN

Key Exclusion:

- Splenic irradiation within 6 months prior to Screening, or prior splenectomy
- Leukemic transformation (> 10% blasts in peripheral blood or bone marrow aspirate/ biopsy)
- Subject is currently on medications that interfere with coagulation (including warfarin) or platelet function within 3 days prior to the first dose of study drug or during the study treatment period with the exception of low dose aspirin (up to 100 mg/day) and low-molecular-weight heparin (LMWH).
- Prior therapy with a BH3 mimetic compound or stem cell transplantation

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Key Exclusion (Continued):

- **Cohort 1b Drug-Drug Interaction (DDI) sub-study subjects only:** Subject has received strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin) or moderate CYP3A inhibitors (e.g., fluconazole) within 14 days prior to the administration of the first dose of study drug.

Investigational Product:	Navitoclax (ABT-263)
Cohort 1a Planned Dose(s):	Dose Level –1: 25 mg once daily Dose Level 1 (Starting Dose): 50 mg once daily Dose Level 2: 100 mg once daily Dose Level 3: 200 mg once daily Dose Level 4: 300 mg once daily
Cohorts 1b, 2 and 3 Planned Dose(s)	Dose Level –3: 25 mg once daily Dose Level –2: 50 mg once daily Dose Level –1: 100 mg once daily (Starting dose; baseline platelet count $\leq 150 \times 10^9$/L) Dose Level 1: 200 mg once daily (Starting dose; baseline platelet count $> 150 \times 10^9$/L) Dose Level 2: 300 mg once daily (after Week 24 for inadequate response)

Intermediate dose levels (e.g., 150 mg, once daily) may be considered for an individual subject at the discretion of the investigator. If intermediate dose levels are utilized prior to Week 24, consultation with the AbbVie TA MD/SD is required prior to implementation.

Mode of Administration:	Oral
Reference Therapy:	Ruxolitinib
Dose(s):	≥ 10 mg twice daily
Mode of Administration:	Oral

Duration of Treatment: Until end of clinical benefit or occurrence of unacceptable toxicity or discontinuation criteria have been met.

Toxicity Management for Thrombocytopenia:

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 below and presented in detail in the toxicity management section of the protocol and Appendix I. Decisions regarding continued dosing, including the navitoclax or ruxolitinib (if applicable) dose level to be administered, for individual subjects will be medically managed by the Investigator in consultation with the AbbVie TA MD/SD.

Dose Adjustment Guidelines for Thrombocytopenia:

See Appendix I for comprehensive guidelines.

Criteria for Evaluation:

Efficacy:

To determine initial disease status, MRI/CT, bone marrow biopsy and aspirate will be obtained at Screening for all subjects. The local bone marrow evaluation will include staining for fibrosis and cytogenetics. To assess for efficacy, bone marrow biopsy, aspirate, MRI/CT, MFSAF and laboratory tests will be performed at designated timepoints throughout the study until disease progression is documented.

Efficacy will be assessed based on modified International Working Group-Myeloproliferative Neoplasms Research and European LeukemiaNet (IWG-MRT/ELN).

Transfusion requirements must be documented during the time period of 12 weeks before the start of navitoclax on Day 1.

Pharmacokinetic:

Pharmacokinetic samples for navitoclax (all cohorts) and ruxolitinib (1a, 1b, and 3) will be collected at designated time points throughout the study.

Biomarkers and Translational Research:

Exploratory research may be conducted to identify biomarkers predictive of navitoclax activity. Peripheral blood and bone marrow samples will be obtained at study specified time points. Biomarkers (e.g., but not limited to: allelic burden, mutational status, BCL-2 family profiling, inflammatory cytokine reduction) may be assessed to compare subject responses in order to identify markers that may be predictive of navitoclax activity alone or in combination with ruxolitinib.

Safety:

Adverse events (AEs), laboratory values, physical examinations, vital signs, and any additional 12-lead electrocardiogram (ECG) performed as clinically indicated will be assessed.

Statistical Methods:

Primary Efficacy Endpoint:

At least 35% reduction from baseline in spleen volume at Week 24 (SVR_{35w24}) as measured by MRI/CT.

Secondary Efficacy Endpoints:

- At least 50% reduction in total symptom score (TSS) at Week 24 from baseline as measured by MFSAF v4.
- Anemia Response.
- Change in grade of bone marrow fibrosis.

Sample Size:

For Cohort 1a, approximately 34 subjects will be enrolled; For Cohort 1b, approximately 80 subjects will be enrolled to ensure enrolment of approximately 70 subjects with prior exposure to ruxolitinib; For Cohorts 2 and 3, approximately 30 subjects to be enrolled into each cohort.

Statistical Methods (Continued):

The table below provides point estimate of SVR_{35w24} Rate and corresponding 95% confidence interval (CI) assuming different response rate scenarios given proposed sample sizes.

Cohort	Sample size	Number of Subjects with SVR_{35w24}	Point Estimate SVR_{35w24} Rate (%)	Exact 95% CI		Half Width of CI
				Lower Limit (%)	Upper Limit (%)	
1a	34	16	47.06	29.78	64.87	17.55
1a	34	18	52.94	35.13	70.22	17.55
1a	34	20	58.82	40.70	75.35	17.33
1a	34	22	64.71	46.49	80.25	16.88
1b	70	32	45.71	33.74	58.06	12.16
1b	70	34	48.57	36.44	60.83	12.19
1b	70	36	51.43	39.17	63.56	12.19
1b	70	38	54.29	41.94	66.26	12.16
2 or 3	30	12	40.00	22.66	59.40	18.37
2 or 3	30	14	46.67	28.34	65.67	18.67
2 or 3	30	16	53.33	34.33	71.66	18.67
2 or 3	30	18	60.00	40.60	77.34	18.37

Based on the table above, this study with proposed sample sizes will provide a reasonable precise estimate of the proportion of subjects with SVR_{35w24} for each cohort. Also, if true probability of experiencing a serious adverse event (SAE) due to the study drug is 10%, then the probability of observing at least one SAE in 34 subjects is more than 97% in Cohort 1a; the probability of observing at least one SAE in 80 subjects is more than 99% in Cohort 1b; and the probability of observing at least one SAE in 30 subjects is more than 95% in either Cohort 2 or 3. Therefore, from safety assessment prospective the proposed sample sizes are adequate.

Pharmacokinetic:

Plasma concentrations and PK parameter values of navitoclax and ruxolitinib will be tabulated for each subject, as applicable, and summary statistics will be computed for each sampling time and each parameter.

Biomarkers and Translational Research:

Exploratory research may be conducted to identify biomarker predictive of navitoclax activity. Peripheral blood and bone marrow samples will be obtained at study specified time points. Biomarkers (e.g., but not limited to: allelic burden, mutational status, BCL-2 family profiling, inflammatory cytokine reduction) may be assessed to compare subject responses in order to identify markers that may be predictive of navitoclax activity alone or in combination with ruxolitinib.

Statistical Methods (Continued):

Safety:

Safety analyses will be performed for all subjects that have received at least one dose of navitoclax unless otherwise indicated. For the study as a whole, AEs will be evaluated by the NCI-CTCAE v. 4.03. Safety will be assessed by evaluating duration of exposure to study drug, adverse events, serious adverse events, deaths, and changes in laboratory tests and vital sign parameters.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BCL-2	B-Cell Lymphoma-2
BCL-X_L	B-Cell Lymphoma Extra Large
BET	Bromodomain and Extra-Terminal motif (BET) proteins
BH	Bcl-2 Homology
BID	Two Times a Day
BM	Bone Marrow
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
COVID-19	Coronavirus Disease – 2019, SARS-CoV-2
CR	Complete Remission
CRF	Case Report Form
CYP3A	Cytochrome P450 3A
CYP2C8	Cytochrome P450 2C8
CYP2C9	Cytochrome P450 2C9
DIPSS	Dynamic International Prognostic Scoring System
DNA	Deoxyribonucleic acid
DTP	Direct-to-patient
ECG	Electrocardiogram
eCRFs	Electronic Case Report Forms
EDC	Electronic Data Capture
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life
ePRO	Electronic Patient Reported Outcome
ET	Essential Thrombocythemia
FDA	Food and Drug Administration
GCP	Good Clinical Practice

IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IWG-MRT/ELN	International Working Group-Myeloproliferative Neoplasms Research and European LeukemiaNet
JAK2/JAK-2	Janus Kinase 2
LDL	Low-density lipoprotein
LMWH	Low-Molecular-Weight Heparin
MCL-1	Myeloid Cell Leukemia 1
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MPN	Myeloproliferative Neoplasm
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NCI-CTAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
OS	Overall Survival
PET-MF	Post-Essential Thrombocythemia Myelofibrosis
PFS	Progression Free Survival
PG	Pharmacogenetic
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PD	Pharmacodynamic
PMF	Primary Myelofibrosis
PPD	Purified Protein Derivative
PO	Orally
PR	Partial Remission
PRO	Patient-Reported Outcome
PPV-MF	Post-Polycythemia Vera Myelofibrosis
PT	Prothrombin Time
PV	Polycythemia Vera

QD	Once a Day
QTcF	QT interval corrected for heart rate by Fridericia's formula
RBC	Red Blood Cell
RNA	Ribonucleic acid
PRBC	Packed Red Blood Cells
SAE(s)	Serious Adverse Event(s)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan
SLL	Small Lymphocytic Lymphoma
SMF	Secondary Myelofibrosis
SUSAR	Suspected Unexpected Serious Adverse Reactions
SVR	Spleen Volume Reduction
SVR_{20}	Spleen Volume Reduction of at least 20%
SVR_{35}	Spleen Volume Reduction of at least 35%
SVR_{35w24}	Spleen Volume Reduction of at least 35% at Week 24
TA MD/SD	Therapeutic Area Medical Director/Scientific Director
TB	Tuberculosis
TCV	Treatment Completion Visit
TSS	Total System Score
ULN	Upper Limit of Normal
WBC	White Blood Cell Count
WHO	World Health Organization

Pharmacokinetic and Statistical Abbreviations

AUC	Area under the plasma concentration-time curve
AUC_{∞}	Area under the plasma concentration-time curve from time zero to infinity
AUC_t	Area under the plasma concentration-time curve from time zero to the last measurable concentration
C_{max}	Maximum observed plasma concentration
T_{max}	Time to maximum observed plasma concentration

2.0 Table of Contents

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3.0 Introduction

3.1 Myelofibrosis

Myelofibrosis (MF) is an acquired clonal Philadelphia chromosome negative myeloproliferative neoplasm (MPN). It can present as primary MF (PMF) or as Secondary MF (SMF) following transformation of Polycythemia Vera (PV) to Post PV-MF (PPV-MF) or Essential Thrombocythemia (ET) to Post ET-MF (PET-MF).[1]

MF is characterized by constitutional symptoms, splenomegaly, an increased risk of transformation to acute myeloid leukemia (AML) and a shortened life expectancy.[2] The median age at diagnosis is in the sixth decade and 90% of patients are diagnosed after the age of 40 years.[3]

Ruxolitinib is approved for the treatment of patients with primary myelofibrosis in the United States and European Union. Ruxolitinib induces improvement in splenomegaly and disease-related symptoms as compared to placebo or best available alternative therapy.[4] However, therapy with ruxolitinib does not eradicate the malignant clones, is not known to improve bone marrow fibrosis, and patients who stop ruxolitinib rapidly become symptomatic again. Some patients do not respond to ruxolitinib, whereas, others develop secondary resistance.[5] Current therapy other than hematopoietic stem cell transplantation (HSCT) are not able to control all the clinical manifestations of MF, therefore, new treatments including combination strategies with ruxolitinib as the backbone are a major focus of clinical research.

3.2 BCL-2 Family Proteins

The BCL-2 family proteins are important regulators of the intrinsic apoptosis pathway. The *BCL2* oncogene was first identified in follicular lymphoma where the t(14;18) chromosomal translocation results in significant over-expression of the protein in B-cells.[6] In contrast to other known oncogenes, BCL-2 does not stimulate cellular proliferation, but rather inhibits programmed cell death by protecting cells from a wide variety of pro-apoptotic stimuli, including cytokine withdrawal, irradiation, cytotoxic drugs, heat

and deregulated oncogenes.[7] The *BCL2* family of genes encodes closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four BCL-2 Homology (BH) domains.[8-12] The anti-apoptotic family members (BCL-X_L, BCL-2, BCL-W, BFL-1/A1 and MCL-1) are characterized by four BH domains that are designated BH1 – 4. The pro-apoptotic family members can be further subdivided into multidomain apoptosis effector proteins (BAX, BAK) and the BH3-only proteins (BAD, BIK, BID, BIM, HRK, BMF, NOXA, and PUMA). The interplay between these three groups of proteins serves to regulate initiation of the intrinsic apoptosis pathway.

The multidomain pro-apoptotic proteins BAX and BAK are direct mediators of apoptosis which, when activated, oligomerize to form pores in the outer membrane of mitochondria, enabling the release of apoptogenic factors like cytochrome *c* into the cytosol. They are absolutely required for the execution of cell death by apoptosis. Anti-apoptotic BCL-2 family proteins (e.g., BCL-2, MCL-1 and BCL-X_L) inhibit cytochrome c release by sequestering BAX and BAK and blocking their activation.[13]

3.3 Navitoclax Activity

Navitoclax (ABT-263) is a novel small-molecule BCL-2 family protein inhibitor that binds with high affinity ($K_i \leq 1$ nM) to BCL X_L, BCL-2, and BCL-W. By competitively binding to these proteins, navitoclax frees pro-apoptotic family members, thus triggering cell death by apoptosis in sensitive populations. Certain cancer cells are particularly sensitive to navitoclax. For example, navitoclax displays potent mechanism-based cytotoxicity ($EC_{50} \leq 1$ µM) against human tumor cell lines derived from small cell lung carcinomas and lymphoid malignancies.[14] Navitoclax exhibits potent single agent activity against 10 of 22 cell lines consisting of multiple leukemia and lymphoma types spanning both B-cell and T-cell malignancies. Navitoclax and its closely related predecessor, ABT-737,[15] have also shown cell killing activity against myeloproliferative neoplasm (MPN) patient samples cultured ex vivo[16] and MPN-derived cell lines bearing the activating JAK2 V617F mutation, which is common in PCV and MF.[17,18] Aberrant JAK2-STAT3/5 signaling has been linked to over-expression of the well-known navitoclax resistance factor MCL-1, and JAK2 inhibitors have been shown to reduce

MCL-1 expression, likely accounting for the synergistic cell killing observed when they were in combination with navitoclax.[18] Conversely, BCL-X_L elevation has been associated with resistance to JAK2 inhibitors, and navitoclax has shown the ability to overcome that resistance.[17] BCL-X_L inhibition alone, achieved using a more selective inhibitor (WEHI-539), was shown to be sufficient for overcoming resistance. Importantly, ABT-737 has also shown an ability to block the proliferation of MPN cells in long-term colony forming assays, which serve as an indicator of malignant precursor/stem cell survival and proliferation. For example, endogenous erythroid colonies representing malignant PV clones able to grow in the absence of erythropoietin (EPO) were significantly inhibited in the presence of 500 nM ABT-737[16] and could be further suppressed when 100 – 300 nM ABT-737 was combined with a JAK2 inhibitor.[19] These data indicate that BCL-2/BCL-X_L inhibitors like ABT-737 and navitoclax have the potential to kill malignant MPN precursors when combined with a JAK2 inhibitor. The addition of navitoclax to a JAK2 inhibitor has also demonstrated enhanced efficacy in animal models of JAK2-mutated malignancies – for example, significantly slowing the growth of tumors in mice bearing the Eμ-TEL-JAK2 transgene or patient-derived xenograft (PDX) mice bearing JAK2-mutated B-ALL cells.[17] The combination was also superior to either agent alone in prolonging the survival of mice with JAK2-mutated tumors, in some cases effecting cures.[17]

The anticipated and observed toxicities to date are mechanism-based, in particular, BCL-X_L mediated decrease in circulating platelet survival and BCL-2 mediated effects on lymphocytes. Nonclinically, testicular germ cell depletion was observed in rats and dogs but only after 6 months of dosing at 100 mg/kg/day (the highest dose tested). The testicular effects of navitoclax are thought to be related to Bcl-w inhibition. Sperm evaluation has not been conducted in the clinic and therefore it is unknown if there has been any decrease in sperm count or alteration in sperm quality.

Navitoclax accelerates apoptosis of circulating mature platelets, which differs from typical chemotherapy induced thrombocytopenia (i.e., toxicity to platelet progenitors in the bone marrow) related to myelosuppression. Limited human clinical data are available to

understand the response to infusion of exogenous platelets in the presence of circulating drug levels. Platelet transfusion studies conducted in beagle dogs demonstrated that transfusion of one-day old platelets administered near the time of navitoclax C_{max}, resulted in higher platelet levels than dogs not receiving supplemental platelets. Platelet concentrations remained higher after 24 hours with declining navitoclax concentrations. This study suggests that infusion of platelets may have beneficial effects in treating acute thrombocytopenia following oral dosing with navitoclax.

From the pre-clinical models, there may be an opportunity in the monotherapy setting to increase efficacy without additional platelet toxicity in the setting of continuous dosing. In murine xenograft models of small cell lung cancer, 21 days of continuous dosing achieves superior tumor growth inhibition, greater increase in life span, and greater incidence of complete and overall response rates compared to the intermittent dosing schedules or 14 days of dosing and 7 days off drug. In a dog toxicology study, navitoclax was delivered once daily for 28 days. At doses that achieve plasma concentrations within the targeted efficacious exposure range, circulating platelet counts recovered to baseline within 14 days of dosing and remained at baseline for the subsequent 14 days of dosing.

This observation of platelet recovery during continued navitoclax dosing has also been observed in the Phase 1 clinical studies. Given that platelet nadirs typically occur in the first few days of dosing and circulating platelet counts recover during continued dosing, a lead-in dosing period may help reduce the depth of platelet nadir.

Also in dogs at high doses, cardiovascular effects (decrease in cardiac output and increase in systemic and pulmonary vascular resistance) have been observed in safety pharmacology assessments. However, results from a follow up 28-day study in dogs suggest that the cardiovascular effects are not exacerbated after multiple days of dosing or after multiple single infusions of platelets.

3.4 Navitoclax Clinical Data

Three Phase 1/2a clinical trials investigating the safety, pharmacokinetics, and efficacy of navitoclax in subjects with relapsed or refractory lymphoid malignancies, subjects with small cell lung cancer or other non-hematological malignancies and subjects with chronic lymphocytic leukemia (CLL) are underway or completed.

Preliminary aggregate clinical data from 2 ongoing Phase 1 studies support that navitoclax is tolerable at doses up to 250 mg in a CLL population and up to 325 mg in a lymphoid malignancy population (which includes CLL/SLL subjects). These studies were utilizing a 21/21 day dosing schedule (subjects dosed for 21 consecutive days of a 21-day cycle following a 7 to 14 day lead-in period). Anti-tumor activity has been noted in study subjects with CLL/SLL across the dose ranges tested, suggesting that navitoclax may provide a clinical benefit to these subjects.

As of 28Feb2020, a total of 34 subjects with MF (Cohort 1a) have been treated in the navitoclax in combination with ruxolitinib in Study M16-109. To date adverse events observed occurred at an incidence that appears to be consistent with what has been observed in navitoclax clinical studies and with this population of patients with MF. The most common adverse events of any Grade in Study M16-109 to date are thrombocytopenia (88%), diarrhea (68%) and fatigue (62%). Serious adverse events were reported in 13 subjects (38%) including pneumonia (n = 4), splenic infarct (n = 2), and the following events with 1 occurrence each: anemia, angina pectoris, abdominal pain, colitis, vomiting, chest pain, pyrexia, biliary colic, hyperbilirubinemia, portal vein thrombosis, abnormal liver function tests, gout, respiratory failure and deep vein thrombosis.

Efficacy data from Study M16-109 is available for 34 subjects (Cohort 1a). Spleen Volume Reductions of ≥ 35% at Week 24 (SVR_{35w24}) were observed in 27% (9/34) of subjects. Improvements in bone marrow fibrosis have been reported in 29% (10/34) of subjects.

For further details, please refer to the Investigator's Brochure for additional information regarding navitoclax clinical studies, safety and efficacy data, pre-clinical toxicology, metabolism, and pharmacology.

3.5 Differences Statement

This is the first study to evaluate navitoclax in subjects with myelofibrosis.

3.6 Benefits and Risks

Conventional treatment includes wait and see approach for asymptomatic patients, erythropoiesis-stimulating agents, androgens or immunomodulatory agents for anemia, cytoreductive drugs such as hydroxyurea for splenomegaly and constitutional symptoms, and splenectomy or radiotherapy for selected patients.[20] Currently, ruxolitinib, a dual JAK-1 and -2 inhibitor, is the only targeted therapy approved for the treatment of myelofibrosis in the United States and European Union. While the approval of ruxolitinib has changed the treatment landscape for patients with myelofibrosis, it is still 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.

Fedratinib, a JAK-2 specific inhibitor, is currently in clinical development and has been evaluated in patients with MF. The reported SVR_{35} with fedratinib in the previously untreated population is similar that reported of ruxolitinib at approximately 40%.[21,22] A recent re-analysis of the JAKARTA-2 study of fedratinib in patients with MF that previously failed ruxolitinib treatment reports a SVR_{35} of 30%. The most common adverse events in the JAKARTA-2 study in the ruxolitinib failure cohort are reported as anemia (100%), platelet count decrease (73%), creatinine increased (72%), diarrhea (65%), nausea (53%), and ALT increased (52%). Additionally, among the 600 subjects treated with fedratinib in clinical trials, 8 subjects were reported to have potential Wernicke's encephalopathy.[23]

Navitoclax has been evaluated in 25 clinical studies as both single-agent and as combination therapy. Clinical studies have assessed the safety, pharmacokinetics and initial efficacy in subjects with hematologic malignancies or in subject with solid tumors. There is preclinical data that suggest that the combination of navitoclax with ruxolitinib may provide disease-modifying therapy for patients with PMF or SMF.

The preliminary data of the combination of navitoclax and ruxolitinib (Study M16-109) in patients with MF that have previously received ruxolitinib are favorable. The spleen response rates of the combination are similar to that observed with fedratinib (JAKARTA-2 study) with an acceptable safety profile for this population. This data supports further evaluation of both the combination in patients with MF that have either not received ruxolitinib or have failed prior ruxolitinib therapy. Additional evaluation of the single-agent activity of navitoclax is also supported given the response rates observed of the combination in a population of patients that had failed prior ruxolitinib treatment.

This study will evaluate the addition of navitoclax to ruxolitinib in patients with PMF or SMF (PPV-MF or PET-MF) with persistent splenomegaly while receiving ruxolitinib monotherapy in Cohorts 1a and 1b. Cohort 2 will evaluate navitoclax alone in patients with PMF or SMF that have splenomegaly and have received prior treatment with a JAK-2 inhibitor. Cohort 3 will evaluate navitoclax in combination with ruxolitinib in patients with PMF or SMF that have not received treatment with a prior JAK-2 inhibitor or BET inhibitor. The initial navitoclax dose and dosing schedule are derived from clinical experience in other indications.

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of navitoclax. The Sponsor has evaluated the potential risks of study participation during a global or regional epidemic and concludes that the potential benefit of the study outweighs the additional risk.

4.0 Study Objectives

The primary objective of the study is to:

- Evaluate the effect of navitoclax alone or in combination with ruxolitinib on spleen volume

The secondary objectives of the study are:

- To assess the effect of navitoclax alone or in combination with ruxolitinib on total symptom score (TSS) as assessed by the Myelofibrosis Symptom Assessment Form (MFSAF) version 4.0 diary
- To evaluate the effect of navitoclax alone or in combination with ruxolitinib on bone marrow fibrosis
- To determine the rate of anemia response associated with navitoclax alone or in combination with ruxolitinib
- To describe the safety profile and PK profile observed with navitoclax alone or in combination with ruxolitinib

The exploratory objectives of the study may include but not limited to:

- To evaluate the effect of navitoclax alone or in combination with ruxolitinib on the onset, magnitude and duration of disease response, including effects on spleen and anemia.
- To evaluate the effect of navitoclax alone or in combination with ruxolitinib on measures of health-related quality of life including total symptom score, fatigue, and physical functioning.
- To evaluate the effect of navitoclax alone or in combination with ruxolitinib on overall survival (OS) and progression free survival (PFS).
- Exploration of biomarkers predictive of navitoclax activity and response may be performed.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 2, multicenter, open-label study designed to evaluate the tolerability and efficacy of navitoclax alone or in combination with ruxolitinib in subjects with primary or secondary myelofibrosis (PPV-MF, PET-MF). Subjects enrolled in Cohort 1a must have received ruxolitinib therapy for at least 12 weeks and currently be on a stable dose of ≥ 10 mg twice daily of ruxolitinib. For Cohort 1b subjects must have received treatment with ruxolitinib. For Cohort 2, subjects must have received prior treatment with a JAK-2 inhibitor. For Cohort 3, subjects must not have received prior treatment with a JAK-2 inhibitor or BET inhibitor.

Approximately 174 subjects at approximately 135 sites globally will be enrolled in the following cohorts:

- Cohort 1a: 34 subjects (fully enrolled as of 10 April 2019)
- Cohort 1b: approximately 80 subjects will be enrolled to ensure enrollment of approximately 70 subjects with prior exposure to ruxolitinib.
- Cohort 2: approximately 30 subjects
- Cohort 3: approximately 30 subjects

The study is designed to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. All efforts will be made to adhere to these specific enrollment numbers; however, it might not be ethical to deny treatment to subjects in Screening as they may have undergone study related procedures. Subjects that are enrolled and do not meet the inclusion criteria as outlined in Section 5.2 may be replaced at the discretion of the Sponsor.

The study will consist of the following:

- **Screening:** Study assessment performed prior to enrollment;

- **Treatment:** Study assessments performed from first dose through the Treatment Completion Visit (TCV);
- **Follow-up:**
  - **Safety Follow-up:** approximately 30 days following TCV to assess adverse events
  - **Post-Treatment Follow-up:** Every 12 weeks after the TCV until disease progression is documented or until another therapy for MF is initiated
  - **Survival:** Every 6 months follow-up for survival status and collection of post-treatment cancer therapy details

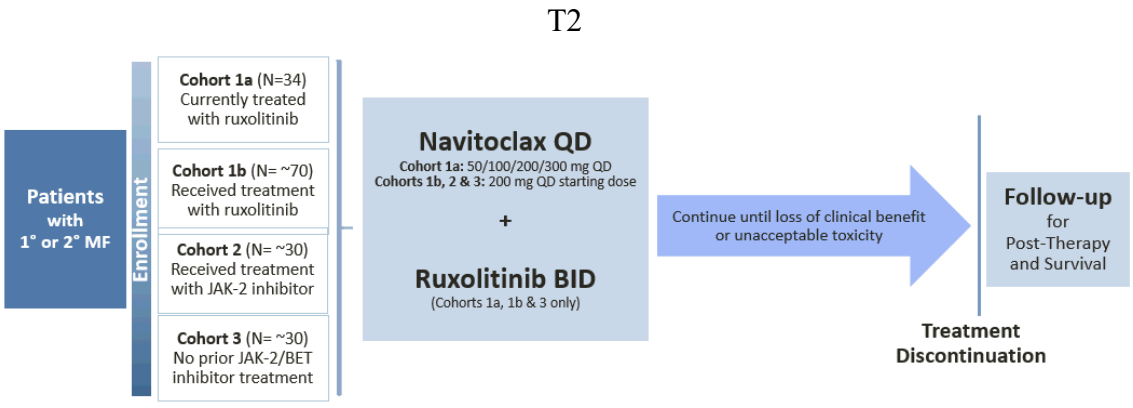
Screening

Unless otherwise specified, Screening assessments must be performed within 28 days prior to first dose of navitoclax. For subjects enrolled in Cohorts 1b and 3, the screening period should be long enough to ensure there is at least 7 days to collect the daily MFSAF v4.0 prior to Day 1.

Treatment

Once Screening procedures are completed and eligibility is confirmed, subjects will begin study treatment. A schematic of the study design is shown below in Figure 1.

Figure 1. Study Schema



All eligible subjects will initiate navitoclax orally (PO) once daily at the starting dose of 50 mg once daily (Cohort 1a) or at 100 mg or 200 mg once daily (Cohorts 1b, 2 or 3).

Cohort 1b will enroll approximately 80 subjects to ensure enrollment of approximately 70 subjects with prior exposure to ruxolitinib.

Cohort 1a

The dose of navitoclax may be increased after approximately 7 or more days to the next dose level provided the platelet count is $\geq 75 \times 10^9$/L up to a maximum dose of navitoclax 300 mg once daily.

Cohorts 1b, 2 or 3

- Baseline Platelet Count $>150 \times 10^9$/L: 200 mg once daily navitoclax starting dose
- Baseline platelet count $\leq 150 \times 10^9$/L: 100 mg once daily navitoclax starting dose
  - The dose of navitoclax may be increased to 200 mg once daily after 7 days provided the platelet count is $\geq 75 \times 10^9$/L
- The dose of navitoclax should not exceed 200 mg once daily for the first 24 weeks of treatment. After the Week 24 disease assessment, the dose of navitoclax may be increased to 300 mg once daily at the discretion of the Investigator for subjects with sub-optimal spleen response defined as failure to achieve spleen volume reduction of at least 10% as assessed by imaging.

If a dose reduction below navitoclax 50 mg once daily is required, the dose of navitoclax may be reduced to 25 mg once daily following consultation with the AbbVie Therapeutic Area Medical Director/Scientific Director (TA MD/SD) (Section 6.1.5).

Subjects in Cohorts 1a, 1b or 3 will receive ruxolitinib administered orally twice daily (BID). Subjects in Cohort 1a and 1b receiving ruxolitinib at screening will continue at the current stable dose of ≥ 10 mg twice daily. Subjects in Cohorts 1b not receiving

ruxolitinib at the time of screening will receive ruxolitinib at a dose of 10 mg twice daily beginning on Day 1. Subjects in Cohort 3 will receive ruxolitinib at the individualized starting dose based on baseline platelet count as per the local approved ruxolitinib label. The dose of ruxolitinib may be reduced during the study to manage toxicities.

Subjects in Cohort 2 will receive Navitoclax monotherapy.

During treatment, all assessments must be performed on the day of the specified visit unless a time window is specified in the schedule of assessments (Appendix C). Refer to Section 3.6 for study visit modifications.

Subjects will continue their treatment until end of clinical benefit, unacceptable toxicity or subject meets other protocol criteria for discontinuation (whichever occurs first). All subjects will have a TCV performed when treatment is discontinued.

Response and progression will be assessed by the Investigator based on the modified International Working Group-Myeloproliferative Neoplasms Research and European Leukemia Net (IWG-MRT/ELN) and as noted in Appendix E.[24] Spleen volume will be assessed by an independent central review and interpretations will be transmitted to investigators, as available, and will be utilized in determining response and progression. The evaluation of fibrosis grading and reticulin staining grading may be assessed independently by a central pathologist. Independent interpretations of bone marrow samples are not planned to be transmitted to investigators. Details regarding the determination of clinical response and disease progression are provided in Appendix E.

Follow-Up

Safety Follow-Up: All subjects will have one Safety Follow-up visit approximately 30 days following TCV.

Post-Treatment Follow-Up: For subjects who discontinue study treatment for reasons other than disease progression, a Post-Treatment Follow-up visit will be performed approximately 12 weeks following TCV, then every 12 weeks thereafter to assess disease

status until criteria are met for discontinuation from study (e.g., disease progression, initiation of post-treatment cancer therapy, or subject refusal of post-treatment follow-up visits).

Once disease progression is confirmed or the subject begins a post-study treatment for MF other than the continuation of ruxolitinib (Cohorts 1a, 1b or 3), the subject will enter the Survival Follow-up phase.

Survival Follow-Up: Survival Follow-up will then be performed approximately every 6 months for up to 5 years after TCV (provided informed consent has not been withdrawn for collection of such information). Survival information (e.g., 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.

5.2 Selection of Study Population

Adult male and female subjects with primary or secondary MF and who meet all inclusion criteria and none of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following criteria:

1. Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any Screening or study-specific procedures.
2. Subject must be ≥ 18 years of age.
3. Subjects with documented diagnosis of Primary MF, PPV-MF, or PET-MF as defined by the World Health Organization classification.
4. Subjects classified as intermediate-2 or high-risk MF, as defined by the Dynamic International Prognostic Scoring System (DIPSS).

5. Subject must be ineligible due to age, comorbidities, or unfit for unrelated or unmatched donor transplantation or unwilling to undergo stem cell transplantation at time of study entry.
6. ECOG 0, 1, or 2.
7. **Cohort 1a only:** Subject must have received ruxolitinib therapy for at least 12 weeks and be on a stable dose of ≥ 10 mg twice daily of ruxolitinib for ≥ 8 weeks prior to the 1st dose of navitoclax.

   Note: Subjects with ruxolitinib dose reductions within 8 weeks prior to study enrollment may be considered on a stable dose if stable at that decreased dose of ruxolitinib for ≥ 2 weeks prior to the 1st dose of navitoclax. If the dose reduction was due to thrombocytopenia, the platelets must be confirmed to be stable by a repeat laboratory test.
8. **Cohort 1b only:** Subject must have received treatment with ruxolitinib and meet at least one of the following criteria:
   a. Prior or current treatment with ruxolitinib for ≥ 24 weeks with lack of efficacy defined as a lack of spleen response (refractory) or a loss of spleen or symptom response (relapsed)
   b. Prior or current treatment with ruxolitinib for < 24 weeks with documented disease progression while on ruxolitinib as defined by any of the following:
      i. Appearance of new splenomegaly that is palpable to at least 5 cm below the left costal margin (LCM) in subjects with no evidence of splenomegaly prior to the initiation of ruxolitinib.
      ii. A ≥ 100% increase in the palpable distance below the LCM in subjects with measurable spleen distance 5 to 10 cm prior to the initiation of ruxolitinib.
      iii. A ≥ 50% increase in the palpable distance below the LCM in subjects with measurable spleen distance > 10 cm prior to the initiation of ruxolitinib.

iv. A spleen volume increase of ≥ 25% (as assessed by MRI or CT scan) in subjects with a spleen volume assessment prior to the initiation of ruxolitinib.

c. Prior or current treatment with ruxolitinib for ≥ 28 days with intolerance defined as new RBC transfusion requirement (at least 2 units/month for 2 months) while receiving a total daily ruxolitinib dose of ≥ 30 mg but unable to reduce dose further due to lack of efficacy.

9. **Cohort 1b only:** Subjects that are receiving ruxolitinib at the time of screening, must currently be on a stable dose ≥ 10 mg twice daily of ruxolitinib for ≥ 4 weeks prior to the 1st dose of navitoclax.

Note: Subjects with ruxolitinib dose reductions within 4 weeks prior to study enrollment are considered to be on stable dose if dose of ruxolitinib is unchanged for ≥ 2 weeks prior to Day 1 of navitoclax. The current dose must be ≥ 10 mg twice daily. If the dose reduction was due to thrombocytopenia, platelet counts must be confirmed to be stable by a repeat laboratory test.

10. **Cohort 1b only:** Subject must not have received treatment with a BET inhibitor or an alternate JAK-2 inhibitor other than ruxolitinib.

11. **Cohort 2 only:** Subject must have received prior treatment with JAK-2 inhibitor therapy and meet one of the following criteria (a or b):

a. Prior treatment with JAK-2 inhibitor for at least 12 weeks

b. Prior treatment with JAK-2 inhibitor for ≥ 28 days complicated by any of the following:

i. Development of red blood cell transfusion requirement (at least 2 units/month for 2 months

OR

ii. Grade ≥ 3 adverse events of thrombocytopenia, anemia, hematoma and/or hemorrhage while on JAK-2 inhibitor treatment

12. **Cohort 3 only:** Subject must not have received prior treatment with a JAK-2 or BET inhibitor.
13. Subject has splenomegaly defined as a spleen palpation measurement ≥ 5 cm below costal margin or spleen volume ≥ 450 cm^3 as assessed by MRI/CT.
14. **Cohorts 1b and 3 only:** Subject has at least 2 symptoms each with a score ≥ 3 or a total score of ≥ 12, as measured by the MFSAF v4.0 on at least 4 out of 7 days during screening prior to study drug dosing.
15. Subject must meet the following laboratory parameters per local laboratory reference range during screening, prior to study drug dosing:
    - Adequate bone marrow reserve; in the absence of growth factors, thrombopoietic factors, or platelet transfusions for at least 14 days:
      - Platelet count ≥ 100 × 10^9/L (Cohorts 1a, 1b or 3)
      - Platelet count ≥ 75 × 10^9/L (Cohort 2)
      - ANC ≥ 1 × 10^9/L
    - Renal function: calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault formula
    - Hepatic function and enzymes:
      - AST and ALT ≤ 3.0 × upper normal limit (ULN)
      - Total Bilirubin ≤ 1.5 × ULN (exception: subjects with Gilbert's Syndrome may have a Bilirubin > 1.5 × ULN)
    - Coagulation:
      - aPTT ≤ 1.5 × ULN
      - Prothrombin time (PT) or INR ≤ 1.5 × ULN
16. 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.

If male, and subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through at least 90 days after the last dose of study drug, to practice the protocol specified contraception (Section 5.2.5).

17. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine or serum pregnancy test on Study Day 1. Negative pregnancy test must be available prior to first dose.

    Females of non-childbearing potential (as defined in Section 5.2.5) at Screening do not require pregnancy testing.

Rationale for Inclusion Criteria

1	In accordance with Harmonized Good Clinical Practice (GCP)
2 – 12, 14	To select the subject population
13, 15	For the safety of the subjects
16 – 17	The impact of the Navitoclax on pregnancy is unknown

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Splenic irradiation within 6 months prior to Screening, or prior splenectomy.
2. Leukemic transformation (> 10% blasts in peripheral blood or bone marrow aspirate /biopsy).
3. Subject is currently on medications that interfere with coagulation (including warfarin) or platelet function within 3 days prior to the first dose of study drug or during the study treatment period with the exception of low dose aspirin (up to 100 mg/day) and LMWH.
4. Prior therapy with a BH3 mimetic compound or stem cell transplantation.

5. Subject has a history of an active malignancy other than MF within the past 2 years prior to study entry, with the exception of:
   - Adequately treated in situ carcinoma of the cervix uteri
   - 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.
6. Subject has a known positive test for HIV.

   Note: HIV testing is not required at Screening.
7. Subject has known hepatitis B (HBV) or hepatitis C (HCV) 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 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).
8. 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.
9. 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).
10. Subject exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    - Ongoing systemic infection (viral, bacterial, mycobacterial or fungal)
      - Active SARS-CoV-2 infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., PCR) test result. Note: SARS CoV-2 diagnostic tests should be applied following local requirements/recommendations.
        - Subjects positive for active SARS-CoV-2 infection may rescreen after they meet either criteria a or b indicating SARS-CoV-2 infection has resolved with viral clearance:

a. At least 14 days since first PCR test result have passed in asymptomatic patients

   OR

b. At least 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

- Cohorts 1b and 3 only: Subject has tested positive for tuberculosis prior to study entry (subjects must have a negative result per local guidelines or have no evidence of latent infection prior to study entry, (see Section 5.3 Tuberculosis Testing for additional details.)
- Febrile neutropenia

11. **Cohort 1b Drug-Drug Interaction (DDI) sub-study subjects only:** Subject has received any of the following **within 14 days** prior to the first dose of study drug:
    - Strong or moderate CYP3A inhibitors (see Appendix H)
12. **Cohort 1b Drug-Drug Interaction (DDI) sub-study subjects only:** Subject has consumed one or more of the following **within 3 days** prior to the first dose of study drug:
    - Grapefruit or grapefruit products
    - Seville oranges (including marmalade containing Seville oranges)
    - Star fruit (carambola)
13. Female subject who is pregnant, breastfeeding or is considering becoming pregnant or donating eggs during the study or for approximately 30 days after the last dose of study drug.

    Male subject who is considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug.
14. Subject has history of a cardiovascular, endocrinologic, hepatic, immunologic metabolic, neurologic, psychiatric, pulmonary, renal disease, or any other condition that in the opinion of the investigator would adversely affect his/her participation in this study or interpretation of study results.

15. Subject is concurrently participating in another therapeutic clinical trial or subject has previously participated in other AbbVie clinical trials conducted in subjects with myelofibrosis.

Rationale for Exclusion Criteria

1 – 5	These criteria were selected to ensure the appropriate subject population with sufficient disease severity for evaluation
6 – 12, 14 – 15	These criteria are to ensure general good health and safety of the subjects
13	The impact of navitoclax on sperm count, the unborn fetus or breast feeding infant is unknown

5.2.3 Enrollment of Subjects Based on Baseline Platelet Count

Cohort 1a only

Given the potential for navitoclax induced thrombocytopenia, the number of subjects with a baseline platelet count between 100 – 150 × 10^9/L and 150 – 200 × 10^9/L will initially be limited to approximately 6 – 8 subjects per platelet range, respectively. Data from at least the first 28 days of enrollment for approximately the first 6 subjects per platelet range enrolled in Cohort 1a will be reviewed by the TA MD/SD and Safety Physician. Upon review of these initial safety data, the sponsor will determine if further enrollment of patients within the specified platelet ranges should continue.

Cohort 2 only

Given the potential for navitoclax induced thrombocytopenia, the number of subjects with baseline platelet count between 75 – 100 × 10^9/L will be limited to approximately 10 subjects. Data from at least the first 28 days of treatment for the first 5 to 6 subjects with lower platelets enrolled in Cohort 2 will be reviewed by the TA MD/SD and Safety Physician. Upon review of these initial safety data, the sponsor will determine if further enrollment of patients within the specified platelet ranges should continue.

5.2.4 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 along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

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.

Best supportive care and treatment will be allowed for each subject (antiemetics, antibiotics, transfusions, nutritional support, pain control, etc.) with the exception of the following:

- Clopidogrel, tirofiban and other anticoagulants, drugs or herbal supplements that affect platelet. Administration of low-dose aspirin (≤ 100 mg daily) and LMWH are allowed; Dose adjustments for LMWH heparin should be made based on the subject's platelet counts and the local label of the agent being used.
- Disulfiram is not allowed during study drug treatment due to potential prolongation of prothrombin time (PT).
- Treatment with NSAIDs for limited duration are permitted during study treatment if the platelet counts > 100×10^9/L.

Anti-cancer therapy including chemotherapy, cytoreductive agents, immunotherapy, radiotherapy, hormonal (with the exception of hormones for thyroid conditions or estrogen replacement therapy), and other investigational agents will not be allowed during study treatment. Hydroxyurea should be discontinued at least 7 days before initiation of navitoclax on Day 1.

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.

For subjects in Cohort 2 receiving treatment with JAK-2 inhibitor therapy prior to study enrollment, a wash-out period is not required. The last dose of the JAK-2 inhibitor therapy must occur ≥ 1 day prior to Day 1 (first dose of navitoclax).

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

Colony stimulating factors (G-CSF, GM-CSF) may be considered during administration of navitoclax if deemed necessary by the investigator.

If clinically indicated, anti-herpes and anti-PCP (Pneumocystis carinii/jiroveci pneumonia) prophylaxis should be considered. Although there is a potential for drug-drug interactions trimethoprim sulfamethoxazole can be considered for PCP prophylaxis with close clinical monitoring.

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 treating physician and the subject.
- The potential impact of navitoclax 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.

  Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.
- These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with myelofibrosis 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.

Subjects Receiving Navitoclax

The following concomitant medications are cautionary during study treatment for subjects receiving navitoclax 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). ***NOTE: Strong and moderate CPY3A inhibitors and foods that inhibit CYP3A as mentioned above are not allowed for subjects participating in the Cohort 1b DDI sub-study.***
- CYP3A inducers such as rifampin and carbamazepine (due to possible induction of the metabolism of navitoclax).

- 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).
- 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).

A sample list of excluded medications and cautionary medications can be found in (Appendix H). Since a complete list of medications that are excluded or 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.

If the investigator determines that use of an excluded or cautionary concomitant medication is medically indicated, the investigator will notify the AbbVie TA MD/SD and discuss the rationale for the use of the concomitant medication and the need to medically monitor the potential study subject under consideration.

Subjects Receiving Ruxolitinib

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 moderate CYP3A4 inhibitors (such as fluconazole) concurrently with ruxolitinib study treatment, the local, approved product label should be referenced for ruxolitinib dose reduction, interruption, and discontinuation, or monitoring guidelines. The local, approved ruxolitinib product label should also be referenced for monitoring guidelines when co-administered with CYP3A inducers or drugs transported by P-gp and BCRP.

5.2.5 Contraception Recommendations

While participating in this research study, subjects should not become pregnant, breastfeed a baby or father a baby.

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:

1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
    - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
    - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
2. Postmenopausal female
    - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
    - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 IU/L.

Females, of Childbearing Potential

- Females of childbearing potential should be provided information from study staff about cryopreservation of eggs prior to treatment with study drug. Review and document pregnancy avoidance recommendations with females of childbearing potential

- Females of childbearing potential must avoid pregnancy while taking study drugs 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 contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy provided a hysterosalpingogram confirms success of the procedure).
  - Vasectomized partner (provided the vasectomized partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).
  - 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 should be provided information to seek advice about cryopreservation of sperm prior to treatment with study drug.

Male subjects who are sexually active with a female partner of childbearing potential, even if the male subject has undergone a successful vasectomy, must agree to use condoms 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 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)

Male subject agrees not to donate sperm from Study Day 1 through at least 90 days after the last dose of study drug.

5.3 Efficacy, Pharmacokinetic, Biomarker, Exploratory Research and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed

Study procedures described are listed in the following section of this protocol and are summarized in tabular format Appendix C.

5.3.1.1 Study Procedures

All study procedures outlined in Appendix C are discussed in detail in this section, with the exception of monitoring of treatment compliance (Section 5.5.4), and adverse event information (Section 6.1.1.1). Unscheduled visits may be performed as medically indicated (e.g., for monitoring of toxicities). All study data, including those from unscheduled visits, will be recorded on electronic case report forms (eCRFs): Patient-Reported Outcome (PRO) assessments will be collected using an electronic and a paper process and recorded into the eCRF.

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed.

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

Activities performed at **site**

- Study Visits and/or activities should be performed as scheduled whenever possible. If an activity, is missed or delayed due to the pandemic, perform the activity at the site at the earliest feasible opportunity.
  - Bone marrow biopsy/aspirate and cytogenetic assessment
  - Imaging for spleen volume assessment
  - Biomarker and exploratory research sample collection
  - Disease response assessment
  - Physical examination: full and targeted exams, including skin examination, and spleen and liver measurement by palpation at Screening and Treatment

Completion visits. A targeted physical examination including skin examination, and spleen and liver measurement by palpation will be conducted during study visits

Activities performed **locally or at site**

- Study Visits and/or activities should be performed as scheduled whenever possible. If activity is missed or delayed due to the pandemic, perform the activity at the site or locally at the earliest feasible opportunity.
  - 12-Lead Electrocardiogram (may be done locally)
  - Clinical laboratory tests (may be done locally)

Activities performed by **Phone/Virtually**

- Some study visits and/or activities may be performed by phone/virtually.
  - Informed consent (if allowed by IRB/EC and/or local guidelines)
  - Adverse event and concomitant medication assessment
  - Transfusion history/status
  - Patient reported outcome assessment PROs eligible for completion by interview at such visits are EORTC QLQ-C30 Version 3, Patient Global Impression of Change, and PROMIS Fatigue Short Form (SF) 7a). Note: The MF-SAF questionnaire should be completed on the ePRO device daily by the patient.
  - ECOG performance status
  - Vital signs (may be obtained by the subject or caregiver as needed)

Screening

Procedures performed at Screening will serve as baseline, unless repeated on Day 1 prior to dosing, in which case the latter will serve as baseline.

Screening procedures must be performed within 28 days prior to initial study drug administration. The 28 day Screening window starts with the signing of the Informed

Consent Form. For subjects enrolled in Cohorts 1b or 3, the screening period should be at least 7 days to ensure adequate duration for collection of the daily of MFSAF v4.0 questionnaire which is needed to calculate a baseline total symptom score. Subjects not meeting inclusion/exclusion criteria will not be enrolled into the study.

Re-Screening

Subjects that initially screen fail for the study may be permitted to re-screen. All Screening procedures, including obtaining informed consent must be repeated, except the MRI/CT and bone marrow biopsy/aspirate from the initial Screening period may be utilized if collected within 35 days of the first dose of study drug, provided the inclusion/exclusion criteria were met. There is no minimum period of time a subject must wait to re-screen for the study. As appropriate, sites are encouraged to discuss subject eligibility with the AbbVie TA MD/SD.

The results of all Screening evaluations must be within medically acceptable limits, upon review by the investigator before a subject can be administered study drug. Subjects will not be enrolled in the study if laboratory or other Screening results are medically unacceptable.

Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative in order to participate in this study. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent must be signed and dated by each subject prior to undergoing any study procedures or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent will also be required for the exploratory research sampling portion of the study and the drug-drug interaction blood sampling for Cohort 1b. Refer to Section 9.3 for details on obtaining and documenting informed consents.

Following signing of ICF, the IRT will be utilized to assign a subject screening number. Subjects who complete all Screening procedures and meet the eligibility criteria in Section 5.2.1 and Section 5.2.2 will proceed to enrollment in IRT.

Subjects will be considered screen failures if the informed consent has been signed and a study-specific procedure has been performed, but subject was not enrolled into the study. The reason for screen failure will be documented in the source and will be captured in the eCRF.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

Medical and Oncologic History

The following will be collected during the Screening Visit per Appendix C:

- Complete medical history, including documentation of any clinically significant medical condition or surgical procedure
- Detailed prior and concomitant medication usage including dates of usage and dosing information for all medications and supplements taken.
- History of tobacco and alcohol use
- Detailed MF disease history including, but not limited to:
  - Prior therapy including start and stop dates, dose and response
  - For subjects that have received prior treatment with ruxolitinib, the spleen measurement (by palpation or imaging) prior to initiation of ruxolitinib, as well as, at the time of response and progression/relapse must be available.
  - Current disease status including Dynamic International Prognostic Scoring System (DIPSS) risk categorization[25] and the DIPSS-Plus risk categorization[26] (Appendix G)
  - Transfusion requirements during the time period of a minimum of 12 weeks before the start of study treatment

On Day 1, any additional medical history observed after signing of the informed consent but prior to initial navitoclax administration and not considered related to study-required procedures will be recorded in the subject's medical history.

Tuberculosis (TB) Testing

The TB screening tests are diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the Investigator to determine if a subject has previous, active, or latent TB. Prior to study enrollment, subjects to be enrolled in Cohorts 1b and 3 will be assessed for evidence of increased risk for TB and tested for TB infection by a purified protein derivative (PPD) skin test and/or interferon-gamma release assay (IGRA). An alternative approved method of testing per local guidelines may also be used. If a subject had a negative TB test within 90 days prior to Day 1 and source documentation is available, the test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases may be discussed with the AbbVie TA MD/SD. The results of the TB test(s) will be retained at the site as the original source documentation. The TB test(s) to be performed depends on local guidelines.

Additional TB test(s) may be performed during the study at the discretion of the investigator per local guidelines. If the test is indeterminate, additional evaluation for latent tuberculosis should be completed per local guidelines before starting ruxolitinib or continuation of ruxolitinib based on the overall risk-benefit determination.

If TB Skin Test is performed, it should be read by a licensed healthcare professional between 48 and 72 hours after administration and the interpretation should be according to standard guidelines. A subject who does not return within 72 hours will need to be rescheduled for another skin test.

Adverse Event and Concomitant Medication Assessment

Any adverse events observed from the signing of the informed consent but prior to initial navitoclax administration will be reported, as serious or non-serious adverse events, if considered by the investigator to be causally related to study-required procedures.

At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event eCRF.

All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing until 30 days following the last dose of study drug.

Bone Marrow and Cytogenetic Assessment

A bone marrow biopsy must be collected along with a bone marrow aspirate (provided the aspirate sample can be collected) and evaluated locally during Screening and as outlined in Appendix C. Cytogenetic analysis should be evaluated at Screening for determination of risk stratification. If cytogenetic analysis was not performed at Screening, a historical result may be utilized for risk stratification determination provided it was obtained within 6 months of Screening and a new therapy was not initiated between the time of collection and Screening. This evaluation will include staining for fibrosis and staining for reticulin grading and cytogenetics. Cytogenetic results from peripheral blood specimen with an adequate number of malignant cells is satisfactory for analysis. Should peripheral blood yield an insufficient number of metaphases analyzed by chromosomal banding analysis (<10), a Fluorescence In Situ Hybridization (FISH) panel for MPN may be used to determine whether the subject has an "unfavorable karyotype," as defined by the DIPSS+, as long as presence of all chromosome abnormalities are assessed: +8; -7/-7q; i(17q); -5/-5q; 12p-; inv(3); 11q23 rearrangement; 20q-; 13q- and 9.

Historical results from bone marrow samples cannot replace the mandatory bone marrow biopsy and aspirate samples obtained and analyzed at Screening.

Bone marrow biopsies and aspirates performed as standard of care during study participation should also be captured on the eCRF. An adequate bone marrow aspirate, if available, will be collected for predictive biomarker assessments.

After 96 weeks of treatment, bone marrow sampling is only necessary to be performed if disease progression is suspected, or at the discretion of the investigator.

For study visits with bone marrow sampling, chemistry and hematology labs should be performed on the same day the bone marrow sample is obtained.

Imaging for Spleen Volume Assessment

Assessment of spleen volume must be performed at Screening with an MRI or a CT scan and as outlined in Appendix C. The scans will be transmitted to the central imaging vendor for an independent central review.

The imaging should be acquired as close as possible to the start of study treatment and must be during the Screening period. Image receipt and verification should be received from the central imaging vendor before the subject can be treated. In the event that the baseline image is determined by the independent reviewer to have been performed incorrectly, the baseline MRI/CT should be rescheduled for the earliest date possible prior to dosing. If imaging is utilized to verify subject eligibility, the baseline spleen volume measurement must be requested and the MRI/CT transmitted at least 7 days prior to planned Day 1 dosing to allow adequate time for delivery of results from the central imaging vendor.

After Week 96, an MRI/CT needs to only be performed if disease progression is suspected.

A non-contrast MRI of the abdomen is the preferred imaging modality. A non-contrast CT scan may be performed if MRI is medically contraindicated due to metallic implants (e.g., pacemaker, prosthetic valves). Subjects should have the same imaging modality performed throughout the study for consistency and direct comparison unless a subject

develops a contraindication to MRI during the course of the study, then a change to CT is permitted. All MRI/CT scans performed during the study must be sent to the central imaging vendor for an independent central review.

Physical Examination

Complete or symptom-directed physical examinations (PE) will be performed at the study visits outlined in Appendix C.

A **complete physical examination** should include the evaluation of the head, eyes, ears, nose, and throat (HEENT); and the following systems: cardiovascular, respiratory, gastrointestinal, musculoskeletal, neurological and dermatological.

A symptom directed physical examination may be limited to those systems associated with symptoms.

All physical examinations should include skin examination, spleen and liver measurement by palpation.

Abnormalities that represent changes from Screening should be documented at each subsequent physical examination. New or worsened abnormalities should be documented as Adverse Events (AEs) if appropriate.

Vital Signs

Body temperature (oral or tympanic), weight, blood pressure, and pulse will be measured at the study visits as outlined in Appendix C.

Blood pressure and pulse should be measured after the subject has been sitting for at least 5 minutes.

Height will be measured only at Screening. The subject should wear lightweight clothing and no shoes during weighing.

ECOG Performance Status

ECOG performance status will be assessed at the study visits outlined in Appendix C as follows:

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

Patient-Reported Outcome (PRO) Assessments

Patient-reported outcomes will be assessed using the MFSAF version 4.0, EORTC QLQ C30, Version 3, the Patient Global Impression of Change (PGIC) and the PROMIS Fatigue Short Form (SF) 7a questionnaires.

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. EORTC QLQ-C30 Version 3, Patient Global Impression of Change, and PROMIS Fatigue Short Form (SF) 7a, PROs are eligible for completion by interview at the subject visit. In this situation, sites will read the PRO questions and response options to the subject and record the subject's responses. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites may share the questionnaire by videoconference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with who collected the information.

MFSAF Version 4.0

MFSAF v4.0 is a symptom diary in which patients rate the following seven MF symptoms: fatigue, night sweats, abdominal discomfort, pruritus, pain under the ribs on the left side, early satiety, and bone pain on a daily basis using a scale from 0 (absent) to 10 (worst imaginable). The TSS reflects the sum of the scores of these symptoms, for a maximum possible score of 70 (ie, most severe symptom experience).

Subjects will be provided with a handheld device at the Screening Visit and should complete the Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 at home around the same time each day during the screening period. All data entered on the device will be immediately stored to the device itself and transmitted to a central server. The investigator and delegated staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt, and confirmation of the study archive.

For subjects enrolled in Cohorts 1b and 3, the investigator/designee should ensure that the subject has completed the MFSAF v4.0 questionnaire on at least 4 of the 7 days prior to the first dose of navitoclax (Day 1). If the investigator believes that the MFSAF v4.0 score on the day before the first dose of navitoclax (Day 1) is not an accurate reflection of the subject's mean symptom score, then the investigator can use the available data to calculate a mean weekly score to determine eligibility. Subjects should then continue to complete the MFSAF daily on the handheld device from the Day 1 visit through the Week 36 visit around the same time each day.

EORTC QLQ-C30 Version 3

Health-related quality of life (HRQoL) and symptoms will also be assessed with the EORTC QLQ-C30 version 3. The EORTC QLQ-C30 is a 30-item subject self-report questionnaire composed of both multi-item and single domains/scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and

six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Subjects will rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." The EORTC QLQ-C30 was developed and validated for use in a cancer patient population, and its reliability and validity is highly consistent across different language cultural groups. A change of 5 to 10 points is considered a small change, and the lower bound (5) is being used to define the minimum important difference. A change of ≥ 10 to < 20 points is considered a moderate change.

Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) scale will be utilized to assess patients' perceptions of change in their myelofibrosis symptoms over time. Patients during study visits will answer the following question: "Since the start of the treatment received in this study, your myelofibrosis symptoms are (1) Very much improved, (2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, (7) Very much worse."

PROMIS Fatigue Short Form (SF) 7a

PROMIS® is a system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being. PROMIS instruments measure concepts such as pain, fatigue, physical function, depression, anxiety and social function. Fatigue will be assessed using the PROMIS Fatigue SF 7a that has been developed and validated for use in oncology populations. The PROMIS Fatigue SF 7a is a seven item questionnaire that assesses the impact and experience of fatigue over the past 7 days. The recommended minimum important difference range is 3 – 5 points; the lower bound (3) is being used as the minimum important difference in this study. All questions employ the following five response options: 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, and 5 = Always. The first six questions are framed in a way that a lower score is associated with a lower level of fatigue. The last question, however, is reverse scored where a lower score means a worse outcome.

These PRO assessments will be collected per Appendix C throughout the trial. PRO assessments should be completed prior to any other clinical assessments and prior to dosing.

Table 1. Patient-Reported Outcome Assessments

Administration Order	Test	Administration Time
1	EORTC QLQ-C30 version 3 (paper)	Approximately 12 minutes
2	PROMIS Fatigue SF 7a (paper)	Approximately 5 minutes
3	PGIC (paper)	Approximately 1 minute
4[a]	MFSAF version 4.0 (electronic)	Approximately 5 minutes

a. This test is performed on a daily basis and may or may not be completed at the clinic.

Pregnancy Testing

- Subjects with borderline pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
- Females of non-childbearing potential (as defined in Section 5.2.5) at Screening do not require pregnancy testing at any time.
- Females of child bearing potential must have a negative serum pregnancy test result at Screening, and a negative urine or serum pregnancy test is required prior to dosing on Study Day 1.
- A urine pregnancy test will also be performed every 4 weeks from Week 4 through Week 24, and then at all visits (Q12W) through treatment completion. Where required by local regulatory authority, urine pregnancy tests will be performed every 4 weeks after Week 24 through treatment completion.
- If the investigator suspects a woman to have become pregnant at any time during the study, additional pregnancy testing should be performed.

Clinical Laboratory Tests

All subjects will undergo laboratory assessments listed in Table 2 per the schedule in Appendix C. Certified local laboratories will be utilized to process and provide results for all assessments listed in Table 2. Local laboratory results should be entered into the eCRF

and these data will be used for all data analysis. The appropriate certifications will be collected from the local laboratories. Laboratory normal ranges will be provided to the AbbVie clinical team, as requested.

The principal investigator or designee should document review (i.e., with initials and date) of all laboratory results after receipt from the local laboratories.

Investigators are encouraged to obtain additional laboratory tests if they believe that an immediate medical intervention may be needed.

The investigator may consider additional hematology lab collection between 72 to 96 hours post-dose for subjects with a lower baseline platelet count or for those that experience a 24-hour platelet count drop of > 40% from the pre-dose platelet count.

Table 2. Clinical Laboratory Tests[a]

Hematology	Clinical Chemistry	Coagulation
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Blasts (if detected)[b] Platelet count (estimate not acceptable) Platelet count by alternate method[c] Ferritin[d]	Blood Urea Nitrogen (BUN) or Urea Creatinine Creatinine Clearance[e] Total bilirubin Conjugated (direct) bilirubin[c] Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Uric acid Total protein Glucose Bicarbonate/CO_2 Chloride C-reactive protein[c] Erythrocyte Sedimentation Rate Gamma-glutamyltransferase[c] Lactate dehydrogenase (LDH)[f]	Prothrombin Time (PT) Activated partial thromboplastin time (aPTT) International Normalized Ratio (INR)
		Lipid Parameters – Fasting State[g]
		Total Cholesterol Low-density lipoprotein (LDL) Triglycerides
		Other[h]
		PPD skin test, or interferon-gamma release assay or other locally approved test for Tuberculosis

a. If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible.

b. WBC differential count and peripheral smear examination for blasts should be performed in the absence of Grade 4 leukopenia. Smear exam for blasts may not be required when unscheduled labs are performed for monitoring thrombocytopenia.

c. Not required, perform as medically indicated.

d. For subjects who received ≥ 4 units of PRBC prior to screening and for subjects who received ≥ 4 units during study treatment.

e Required at Screening but can be performed at investigators discretion during the study.

f. Required at Screening, Week 12, 24, 48, 72, and 96. Optional at all other visits.

Table 2. Clinical Laboratory Tests[a] (Continued)

g. Required for subjects enrolled in Cohorts 1a, 1b or 3 at Screening and Week 12.
h. Prior to study enrollment for subjects to be enrolled in Cohorts 1b and 3.

For any laboratory test value outside the reference range that the investigator considers clinically significant:

- The investigator may repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study or requires a subject to receive treatment, meets protocol specific criteria (see Section 6.1.7 regarding toxicity management), and/or the investigator considers clinically significant will be recorded as an adverse event.

Chemistry and Hematology

Chemistry and hematology will be performed at the study visits outlined in Appendix C and as needed throughout the study. Additionally, hematology will be collected:

- Predose and 4 hours after the first dose of navitoclax on Day 1 and at 24-hours post-first-dose on Day 2,
- Prior to navitoclax dose increases, navitoclax reductions (if during a clinic visit) or re-initiation of navitoclax after interruption.
- Additional time points in Appendix C through the end of the study

Chemistry and hematology labs should always be performed on the same day a bone marrow sample is obtained.

Coagulation

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) samples will be collected as outlined in Appendix C and as needed throughout the study.

Lipid Monitoring (Cohorts 1a, 1b or 3 only)

Treatment with ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL), and triglycerides. Any clinically significant changes in lipid parameters should be monitored and treated according to institutional guidelines for the management of hyperlipidemia.

12-Lead Electrocardiogram (ECG)

A single 12-lead resting ECG will be obtained at Screening, Week 4 (Day 29), Treatment Completion Visit, and as clinically needed. In the event Week 4 or Treatment Completion visit ECG cannot be performed due to travel and other restrictions related to the COVID-19 pandemic, perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG for the subject.

Electrocardiograms will be recorded after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain completely stationary (no talking, laughing, deep breathing, sleeping, or swallowing) for approximately 10 seconds during the ECG recording. While ECGs are being acquired, subjects and staff are prohibited from having devices (e.g., cellular telephones, fans, heaters, etc.) that emit radiofrequency signals in the room.

Each ECG will be printed and evaluated by an appropriately qualified physician at the study site (the "local reader") who will determine if any findings outside normal physiological variation are clinically significant. The local reading of the ECG will be used by the investigator for subject safety assessments, including adverse event

determination and management, and decision on whether a subject will be discontinued from the study.

The local reader will sign and date the safety ECG and provide a global interpretation using the following categories:

- Normal ECG
- Abnormal ECG – Not clinically significant (NCS)
- Abnormal ECG – Clinically significant (CS)
- Unable to evaluate

All local reader evaluations of ECGs will be entered into the electronic source documents; electronic case report forms (CRFs). If the global interpretation is abnormal (NCS or CS), the local reader will provide further information (e.g., sinus bradycardia, arrhythmia). The QT interval corrected for heart rate using Fridericia's formula (QTcF) will be calculated for all ECGs and documented only if the QT interval is determined to be prolonged by the local reader.

All ECG source documentation will be retained at the study site. The automatic cardiograph reading (i.e., cardiograph-generated measurements and interpretations) will not be collected for analysis.

Disease Response Assessment

Assessment of disease response will be evaluated based on the modified International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report (Appendix E).[27] Subject's response is based on the most recent physical examination including palpable measurement of spleen and liver, bone marrow results, questionnaires, imaging and recent hematology values.

For disease response assessments performed at Week 36 and 72, a repeat bone marrow biopsy is not required unless disease progression is suspected. The prior bone marrow assessment may be used for the purposes of assessing disease response.

Assessment of disease response is not required after Week 96 unless disease progression is suspected.

5.3.1.2 Meals and Dietary Requirements

The absorption of ruxolitinib is not affected by food and ruxolitinib may be taken with or without food.

Food increases the bioavailability of navitoclax independent of meal type (low-fat versus high-fat). Therefore, navitoclax should be taken within 30 minutes of food intake.

Cohort 1b Drug-Drug Interaction (DDI) sub-study subjects only: Subjects may not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruit within the 3-day period prior to the first study drug administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

5.3.1.3 Collection and Handling of Biomarker and Exploratory Research Samples

Whole blood, plasma, bone marrow aspirate, and bone marrow core biopsy tissue will be collected per Appendix C. Specimens collected for these purposes may be utilized to evaluate known and/or novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status, related conditions or to evaluate the association with pharmacokinetics, safety or efficacy. All samples should be prepared, labeled, and shipped as outlined in the study-specific laboratory manual. The biomarker rationale is discussed in the Biomarker Research Variables Section (Section 5.3.6).

AbbVie (or people or companies working with AbbVie) will store the biomarker and exploratory research samples in a secure storage space with adequate measures to protect

confidentiality. The samples will be retained while research on navitoclax (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Blood Collections:

Whole blood will be collected into appropriately labeled tubes and processed as outlined in the most current version of Study M16-109 Laboratory Manual.

- Mandatory Blood Collections:
  - **Blood for Plasma:** Approximately 4 mL of blood will be collected at the study visits as outlined in Appendix C.
  - **Blood for Mutational Profiling:** Approximately 4 mL of blood will be collected at the study visits as outlined in Appendix C.
  - **Blood for Allelic Burden:** Approximately 4 mL of blood will be collected at the study visits as outlined in Appendix C.
  - **Blood for Translational Research-Heparin:** Approximately 6 mL of blood will be collected at the study visits as outlined in Appendix C.
  - **Blood for Translational Research-ACD** (Females only enrolled at US sites): Approximately 8.5 mL of blood will be collected at the study visits as outlined in Appendix C.
  - **Blood for Flow Cytometry:** Approximately 5 mL of blood will be collected at the study visits as outlined in Appendix C.
  - **Blood for Viable PBMC:** Approximately 10 mL of blood will be collected at the study visits as outlined in Appendix C.
- Optional Exploratory Research Blood Collections:
  - **Blood for Pharmacogenetic Analysis (optional test and requires informed consent):** Approximately 6.5 mL of blood will be collected for DNA and RNA isolation at the study visits as outlined in Appendix C. Sample collection should occur unless precluded by local regulations.

Bone Marrow Aspirate and Biopsy Collections:

Screening and on-treatment bone marrow aspirate (BMA) and bone marrow biopsy should be collected into appropriately labeled containers in conjunction with the clinical assessments. A portion of the aspirate must be processed according to the institutional standard procedures for clinical evaluation; however, approximately 4 mL of the bone marrow aspirate should be collected for biomarker assessments. Additionally, a portion of the biopsy should be collected for biomarker assessments. Detailed processing will be as outlined in the most current version of the Study M16-109 Laboratory Manual for the following:

- **BMA Mutational Profiling:** Approximately 1 mL of bone marrow aspirate will be collected at study visits as outlined in Appendix C.
- **BMA Translational Research:** Approximately 3 mL of bone marrow aspirate will be collected at study visits as outlined in Appendix C.
- **Bone Marrow Biopsy IHC and Translational Research:** Either an FFPE block or 14 to 20 slides from the diagnostic/response assessment biopsy should be collected for analysis at study visits as outlined in Appendix C.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for navitoclax (3 mL for each timepoint) and ruxolitinib, if applicable, (3 mL for each timepoint) assay will be collected by venipuncture into 3 mL evacuated potassium EDTA-containing collection tubes according to the schedule in Appendix C, Table 7. Subjects in Cohort 1b who agree to participate in the collection of additional blood sampling to evaluate drug-drug interactions between ruxolitinib and navitoclax will have additional blood samples collected at the times as outlined in Appendix D. The date and time of the PK sample collection and the date and time of the last two doses of navitoclax and/or ruxolitinib at each visit will be captured on the eCRF.

5.3.2.2 Handling/Processing of Samples

Blood Samples for Navitoclax PK Assay (All Cohorts)

Detailed sample collection and processing instructions for the navitoclax PK will be provided in the current Study M16-109 laboratory manual.

Blood Samples for Ruxolitinib PK Assay (Cohorts 1a, 1b and 3)

Detailed sample collection and processing instructions for the ruxolitinib PK will be provided in the current Study M16-109 laboratory manual.

5.3.2.3 Disposition of Samples

The frozen plasma PK samples for navitoclax and possible metabolite(s) assay and frozen plasma samples for PK samples for ruxolitinib assay will be packed in dry ice sufficient to last during transport and shipped from the study site to a central lab designated by AbbVie. An inventory of the samples included will accompany the package. Please refer to current Study M16-109 laboratory manual for complete shipping instructions.

5.3.2.4 Measurement Methods

Plasma concentrations of navitoclax will be determined by the Bioanalysis Department at AbbVie using a validated method. Plasma concentration of possible navitoclax metabolite(s) may be determined with validated or non-validated methods.

Plasma concentration of ruxolitinib will be determined under the supervision of the Bioanalysis Department at AbbVie.

5.3.3 Efficacy Endpoints

Primary Endpoints

The primary efficacy endpoint is at least 35% reduction from baseline in spleen volume at Week 24 (SVR_{35W24}) as measured by MRI/CT.

Secondary Endpoints

Secondary efficacy endpoints are as follows:

- At least 50% reduction in TSS at Week 24 from baseline as measured by MFSAF version 4.0
- The anemia response
- Change in grade of the bone marrow fibrosis according to the European consensus grading system[36] (Appendix F)

Exploratory Endpoints

Exploratory efficacy endpoints may include, but are not limited to:

- At least 35% reduction in spleen volume from baseline (SVR_{35}) as measured by MRI or CT scan, per modified IWG criteria at any time point during study
- Duration of SVR_{35}
- At least 50% reduction in palpable splenomegaly from baseline per modified IWG criteria
- At least 50% reduction in TSS at any time point from baseline as measured by MFSAF v4.0
- Change from baseline in TSS
- Red blood cell transfusion during study treatment
- Duration of anemia response
- Exploratory analyses of the MFSAF v4.0, PROMIS Fatigue SF 7a, and EORTC QLQ-C30
- Overall response per modified IWG criteria
- PFS per modified IWG criteria
- OS

5.3.4 Safety Variables

AbbVie will assess adverse events, laboratory data, physical examinations, vital signs and ECGs throughout the study. Adverse events intensity and laboratory evaluation changes will be assessed by utilizing NCI CTCAE Version 4.03.

5.3.5 Pharmacokinetic Variables

Values for the pharmacokinetic parameters of navitoclax, potential navitoclax metabolite(s), and ruxolitinib (if applicable), including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), and the area under the plasma concentration-time curve (AUC) from time 0 to the time of the last measurable concentration (AUC_t) will be determined using non-compartmental methods. Other parameters such as the terminal phase elimination rate constant (β) and the area under the plasma concentration-time curve from time 0 to infinite time (AUC_∞) will be determined if the data warrants.

5.3.6 Biomarker Variables

Biomarker Samples

Biospecimens (whole blood, plasma, bone marrow core biopsy and bone marrow aspirate) will be collected to conduct exploratory biomarker research. Types of biomarkers analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. These assessments may include biomarkers related to the pathway targeted by the study drug or those believed to be related to the disease or to drug response. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to myelofibrosis, and/or in the development of new therapies and diagnostic tests. The analyses are exploratory in nature, may be conducted in non-Good Laboratory Practice (GLP) laboratories, and the results may not be included with the clinical study report.

Plasma may be analyzed for changes in inflammatory cytokines as well as other factors to identify predictive or prognostic biomarkers of efficacy. Additionally, mutational

analysis can provide critical information on the genes involved in tumorgenesis that may be either prognostic or predictive of the response to therapy. Given the targeted nature of navitoclax for a subset of anti-apoptotic proteins (Bcl-2, Bcl X_L, and Bcl-w), the relationship between sensitivity of cell lines to navitoclax and the expression levels of the Bcl-2 family members have been examined in human tumor cell lines. Bcl-2 expression levels (mRNA and protein) exhibited strong correlations with sensitivity, and the protein concentrations of Bcl-X_L paralleled that of Bcl-2. Conversely, higher expression levels (mRNA and protein) of Mcl-1 were associated with resistance. Taken together, preclinical data suggests that tumor cells sensitive to navitoclax will exhibit high Bcl-2 and Bcl-X_L expression coupled to low Mcl-1 expression whereas the inverse could be reflective of navitoclax resistance. Consequently, tumor specimens obtained from blood, and/or bone marrow aspirates/core biopsies prior to therapy and at relapse may be evaluated for relative expression of the Bcl-2 family members using immunohistochemistry (IHC) or sequencing techniques. Additionally, reticulin and collagen staining of core biopsies may be performed to assess the effect of treatment within the bone marrow.

Pharmacogenetic Samples

Pharmacogenetic samples may be analyzed to understand the genetic factors contributing to the subject's myelofibrosis and response to treatment. Genetic factors may include sequencing, gene expression and epigenetic analysis of genes associated with myelofibrosis, myeloproliferative diseases, drug metabolism, drug transport, the drug target pathway, or drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in myelofibrosis, myeloproliferative diseases, response to navitoclax or drugs of this class. The samples may also be used for the development of diagnostic tests related to myeloid dysplasia, myeloproliferative diseases, navitoclax or drugs of this class. The results of pharmacogenetic analyses may not be reported with the study report.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study (study treatment and/or follow-up) at any time. In addition, the Investigator may discontinue a subject from treatment at any time for any reason if the Investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol.

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 within this protocol.

Each subject will be withdrawn from study treatment (as applicable) if any of the following occur:

- The subject has disease progression as defined in Appendix E, and the Investigator feels the subject is no longer benefiting from treatment.
- The subject requires alternative therapy for treatment of MF.
- The subject experiences treatment toxicity which, in the Investigator's opinion, prohibits further therapy or the Investigator believes it is otherwise in the best interest of the subject.
- Significant subject noncompliance with study drug administration, study procedures or study requirements.
- Subject becomes pregnant or begins breastfeeding.
- The subject decides to withdraw consent of being treated by study treatment for any reason.
- Any other medical reason that AbbVie or the study Investigator deems appropriate.

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

In the event that a subject discontinues study treatment, the reason(s) for the discontinuation and the primary reason will be recorded and a TCV will be performed as soon as possible after discontinuation from study treatment.

If a subject is discontinued from study treatment or the study with an ongoing adverse event, the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the adverse event is achieved.

A Safety Follow-Up Visit should be performed for all subjects approximately 30 days following last dose of navitoclax. If the TCV was conducted ≥ 30 days after last dose of navitoclax, the Safety Follow-Up visit does not need to be performed. If the subject refuses or is unable to attend the Safety Follow-Up Visit, this should be noted in the subject's source documentation.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of the study drug must be discontinued immediately. The Investigator must report a pregnancy within 1 working day of the site being aware to one of the AbbVie representatives listed in Section 6.1.5.

Subjects who permanently discontinue study treatment within the first 28 days on study may be replaced at the Sponsor's discretion.

5.4.2 Termination of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or a specific cohort of the study or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

If, in the judgment of the investigator and AbbVie, the continued exposure to the study drug represents a significant risk to subjects, the study will be stopped. The following procedures for termination will be followed:

- If the Sponsor has decided to prematurely terminate the study or a specific cohort of the study, the Sponsor will promptly notify in writing each Investigator as well as regulatory authorities of the decision and give detailed reasons for the discontinuation.
- Each Investigator must promptly notify the IRB/IEC and give detailed reasons for the termination.
- Each Investigator must promptly notify the enrolled subjects of the premature termination and administer appropriate treatments such as replacement of protocol therapy, if applicable, by other appropriate regimens.

5.5 Treatments

5.5.1 Treatments Administered and Dosing

Navitoclax

Subjects will self-administer navitoclax orally in the morning. Tablets must be swallowed whole and must not be broken, chewed, or crushed. On days that pre-dose pharmacokinetic sampling is required, dosing will occur in the morning in the clinic and, if applicable, at the same time as ruxolitinib dosing (Cohorts 1a, 1b, and 3) to facilitate pharmacokinetic sampling.

Subjects will receive the following:

- Cohort 1a: Navitoclax at starting dose of 50 mg once daily, then increased after approximately 7 days to 100 mg, 200 mg, and 300 mg once daily depending on individual tolerability and platelet count.
- Cohorts 1b, 2 and 3:
  - Baseline Platelet Count > 150×10^9/L: 200 mg once daily navitoclax starting dose

- Baseline platelet count ≤ 150 × 10^9/L: 100 mg once daily navitoclax starting dose
  - The dose of navitoclax may be increased to 200 mg once daily after 7 days provided the platelet count is ≥ 75 × 10^9/L
- The dose of navitoclax should not exceed 200 mg once daily for the first 24 weeks of treatment. After the Week 24 disease assessment, the dose of navitoclax may be increased to 300 mg once daily at the discretion of the Investigator for subjects with sub-optimal spleen response defined as failure to achieve spleen volume reduction of at least 10% as assessed by imaging.

Dose modifications will be based on the toxicity management guidelines (Section 6.1.7).

If vomiting occurs within 15 minutes of taking navitoclax and all expelled tablets are still intact, another dose may be taken, and this should be documented. Otherwise, no replacement dose is to be taken.

A missed dose of navitoclax should be taken with food and water within 8 hours of the missed dose. After 8 hours, the missed dose should not be taken. The next dose of navitoclax will be the regularly scheduled dose.

Ruxolitinib (Cohorts 1a, 1b, and 3)

Subjects enrolled in Cohorts 1a, 1b or 3 will self-administer ruxolitinib at prescribed dose. For subjects enrolled in Cohort 1a, the current stable dose of ruxolitinib ≥ 10 mg twice daily will be continued.

For subjects enrolled in Cohort 1b, the dose of ruxolitinib will be administered at the current stable dose of ruxolitinib ≥ 10 mg twice daily for subjects receiving ruxolitinib at screening. For subjects not taking ruxolitinib at the time of screening, ruxolitinib will be administered at a dose of 10 mg twice daily beginning on Day 1.

For subjects enrolled in Cohort 3, ruxolitinib will be administered beginning on Day 1 at the individualized starting dose based on baseline platelet count as per local approved ruxolitinib label. The starting dose may be adjusted at investigator discretion as medically appropriate in consultation with the TA MD/SD with subsequent increase in dose as described in Appendix I.

Dose reductions should be implemented per the approved ruxolitinib local label; refer to the management of toxicities (Section 6.1.7).

Decisions regarding continued dosing, including the navitoclax or ruxolitinib dose level to be administered and increasing the dose of ruxolitinib higher than the starting dose, for individual subjects will be medically managed by the investigator in consultation with the AbbVie TA MD/SD.

On days with pre-dose pharmacokinetic sampling required, dosing of navitoclax and ruxolitinib will occur in the morning in the clinic to facilitate pharmacokinetic sampling.

5.5.2 Identity of Investigational and Standard of Care Medicinal Products

5.5.2.1 Identity of Investigation Products

Information about the navitoclax formulation to be used in this study are presented in Table 3.

Table 3. Identity of Investigational Products

Type of Product	Product Name	Dosage Form	Strength	Route of Administration	Manufacturer
Investigational Product	Navitoclax	Film-Coated Tablets	25 mg and 100 mg	oral	AbbVie

AbbVie will provide the investigational product, navitoclax.

5.5.2.2 Identity of Standard of Care Medicinal Products

Information about the ruxolitinib formulation to be used in this study is presented in Table 4.

Table 4. Identity of Standard of Care Medicinal Products

Type of Product	Product Name	Dosage Form	Strength	Route of Administration	Manufacturer
Standard of Care Medicinal Product	Ruxolitinib	Tablets	5, 10, 15, 20, and 25 mg	oral	Incyte/Novartis

Ruxolitinib tablets will be sourced locally by sites (from a license pharmacy or wholesaler) or provided by AbbVie, depending on country/local regulations. Each site will be responsible for maintaining records including product description, manufacturer, and/or lot numbers for all standard of care medicinal products dispensed by the site.

5.5.2.3 Packaging and Labeling

Navitoclax tablets will be packaged in HDPE (high density polyethylene) plastic bottles to accommodate the study design.

Study Drug provided by AbbVie will be labeled as required per country requirements. Labels must remain affixed to the bottle. All blank spaces on the label will be completed by the site staff prior to dispensing to the subjects.

5.5.2.4 Storage and Disposition of Study Drug

The investigational products supplied in this study are for investigational use only, and are to be used only within the context of this study. All clinical supplies must be maintained under adequate security until dispensed to subjects. All clinical supplies must be stored per the conditions specified on the label.

A storage temperature log is to be maintained to document proper storage conditions. Malfunctions or temperature excursion must be reported to the Sponsor immediately using the AbbVie Temperature Excursion Management System (ATEMS). Study medication should be quarantined and not dispensed until AbbVie (ATEMS) deems the medication as acceptable.

Navitoclax

Navitoclax study drug must be stored at 2° to 25°C (36° to 77°F).

Ruxolitinib

Ruxolitinib tablets must be stored under the conditions specified on the label per local requirements or Summary of Product Characteristics (SmPC).

5.5.3 Blinding

This is an open-label study.

5.5.4 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. Sites may dispense additional study drug when subject is on site, to eliminate the need for a visit due to COVID-19.

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.

Study drug may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the study drug shipped directly to their home
- Shipments may also include other study supplies (e.g., drug dosing diaries, paper copies of PROs). Instructions will be provided by AbbVie as to how a study site can initiate a DTP. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
- AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

An IRT system will assign the study drug provided by AbbVie to be dispensed to a subject during the study. Prior to each scheduled visit, site personnel must contact IRT for the next study drug assignment. AbbVie or its designee will provide specific instructions on the use of IRT.

To document compliance with the treatment regimen, subjects will be instructed to return all study drug bottles/blister packs (empty, partially filled or full), to the study site personnel prior to each visit and at the TCV. The site staff will document the bottles returned and the number of tablets per bottle. Compliance below 80% will require counseling of the subject by study site personnel.

5.5.5 Drug Accountability

The Investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study. Documentation of the receipt of supplies will be supported by a signed and dated Proof of Receipt or similar document. A current (running) and accurate inventory of study drug will be kept by the site and will include lot number, Proof of Receipt number(s), bottle numbers, and the date on which study drug is dispensed to the subject. An overall accountability of study drug will be performed and verified by AbbVie or the designated monitor(s) throughout the study and at the study site Closeout Visit. Upon completion or termination of the study, all original containers (containing partially used or unused study drug) will be returned to AbbVie according to instructions from AbbVie or the designated monitor(s). If prearranged between AbbVie and the site, destruction of used and unused study drug bottles will be performed at the site. Empty containers will be destroyed at the site. Labels must remain attached to the containers.

The site will record the dose of Ruxolitinib prescribed to each subject in the source documents and on the eCRF. When the Investigator obtains Ruxolitinib commercially, site inventory and accountability will not be performed, and drug accountability forms will not be provided by the sponsor.

5.6 Discussion and Justification of Study Design

Ruxolitinib has shown clinical benefit in improving splenomegaly and symptoms in subjects with intermediate or high-risk primary or secondary MF and is the current standard of care. However, only approximately 40% of patients achieve a reduction in spleen volume by ≥ 35% and these improvements are typically observed within the first 12 to 24 weeks of administration if they are to occur.[21] While ruxolitinib improves splenomegaly and disease-related symptoms, it does not impact the underlying fibrosis in the bone marrow. New treatments are still needed with the potential to modify the course of the disease. The combination of navitoclax and ruxolitinib in patients that have failed prior ruxolitinib therapy indicates the potential to induce a spleen response as well as

improve the fibrosis in the bone marrow. Therefore, the evaluation of the combination in patients with MF that have not received prior treatment with a JAK-2 inhibitor represents a reasonable combination to be evaluated in Cohort 3.

Additionally, of those that do derive clinical benefit from ruxolitinib treatment, splenomegaly and symptoms may return despite continued ruxolitinib treatment with approximately half of MF patients discontinuing ruxolitinib within 2 – 3 years.[28,29] In order to address this unmet clinical need, the addition of navitoclax to ruxolitinib in patients with sub-optimal response to ruxolitinib represents a rational combination to be evaluated in Cohorts 1a and 1b. By enrolling subjects who received at least 12 weeks of ruxolitinib or another JAK-2 inhibitor and have an inadequate response, it can be inferred that clinical benefits observed while receiving study treatments are likely due to the addition of navitoclax because continued improvements after 12 weeks of ruxolitinib/JAK-2 inhibitor treatment are unexpected.

The preliminary efficacy analysis of the combination of navitoclax and ruxolitinib in patients that have failed prior ruxolitinib therapy is favorable with a spleen response rate of 29% at Week 24. Given this population has received prior ruxolitinib for at least 12 weeks, no further benefit from ruxolitinib alone was expected. Therefore, the evaluation of navitoclax as a single-agent in Cohort 2 is reasonable to further explore the mechanism of navitoclax response.

5.6.1 Appropriateness of Measurements

Standard PK, statistical, clinical and laboratory procedures will be utilized in this study. The efficacy measurements in this study are standard and validated.

The PRO tools chosen for this study have been widely utilized in cancer research. The MFSAF version 4.0 instrument specifically measures Myelofibrosis-specific symptoms and was developed on the basis of prior versions of Myelofibrosis symptom assessment forms.[24,30] EORTC QLQ-C30 was developed and validated for use in a cancer patient population, and its reliability and validity is highly consistent across different language

cultural groups.[31] Fatigue will be assessed using the PROMIS Fatigue SF 7a that has been developed and validated for use in oncology populations.[32,33] The PROMIS Fatigue SF 7a is a 7-item questionnaire that assesses the impact and experience of fatigue over the past 7 days.

5.6.2 Suitability of Subject Population

JAK-2 inhibition induces down-regulation of the anti-apoptotic protein MCL-1 suggesting a role for navitoclax, a BCL-X_L inhibitor, in the treatment of MPNs including MF.[18] Therefore, subjects diagnosed with MF (PMF or SMF) represent the target population for this study.

5.6.3 Selection of Doses in the Study

Thrombocytopenia observed during ruxolitinib treatment is generally reversible with dose reduction or dose interruption. Subjects enrolled in Cohort 1a and for subjects in Cohort 1b receiving ruxolitinib at the time of screening, will continue the stable dose of ruxolitinib ≥ 10 mg twice daily.

Subjects enrolled in Cohort 1b that are not receiving ruxolitinib at the time of screening will initiate ruxolitinib starting on Day 1 at the dose of 10 mg twice daily. The dose of 10 mg twice daily was selected for this population not receiving ruxolitinib based on the preliminary analysis of the combination of navitoclax and ruxolitinib in Study M16-109 (Cohort 1a). Of the 34 patients enrolled, 25 (74%) patients began study on doses of ruxolitinib > 10 mg twice daily. Of those 25 patients, 22 (88%) patients subsequently dose reduced ruxolitinib to ≤ 10 mg during study treatment. The primary reasons for ruxolitinib dose reductions are thrombocytopenia (55.9%) and anemia (11.9%). The preclinical data suggests that navitoclax may overcome JAK-2 resistance and therefore, re-sensitizing cells to JAK-2 inhibition from ruxolitinib.[17] It is reported that a final titrated ruxolitinib dose of 10 mg twice daily induces spleen volume reductions and is associated with maximal symptom improvement.[34] Therefore, a lower starting dose of ruxolitinib at 10 mg twice daily in patients not receiving ruxolitinib prior to entering the study, is rational when combining with navitoclax.

Subjects in Cohort 3 will receive ruxolitinib at the individualized starting dose based on baseline platelet count as per the local approved ruxolitinib label.

As a BCL-X_L inhibitor, navitoclax can also cause thrombocytopenia via intravascular apoptosis of platelets. AbbVie internal data indicates 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 reason for ruxolitinib dose reductions.[34]

Preliminary data from Study M16-109 Cohort 1a showed that weekly navitoclax dose escalation from 50 mg QD to 300 mg QD 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 Cohort 1a, 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 QD 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 platelet 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 flat starting doses of navitoclax (100 to 300 mg QD)
- Starting at 100 mg QD with a weekly ramp-up to 200 mg QD

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 QD 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 QD or 100 mg QD based on baseline platelet counts.

To minimize the risk of relevant thrombocytopenia, a lower starting dose of 100 mg QD for subjects with a baseline platelet count $\leq 150 \times 10^9$/L was proposed. For subjects with a baseline platelet count of $\leq 150 \times 10^9$/L, the dose of navitoclax will be increased to 200 mg QD after approximately 7 or more days, provided the platelet count remains $\geq 75 \times 10^9$/L.

6.0 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 after it is released for distribution.

The investigational product in this study is defined as navitoclax. Complaints associated with this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1.2 through 6.1.7. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide another cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient 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 accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. 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 6.1.7 regarding toxicity management) and/or if the investigator considers them to be adverse events.

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 preexisting condition and the surgery/procedure has been pre planned prior to study entry. However, if the preexisting 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.

A treatment-emergent adverse event is defined as any adverse event reported by a subject with onset or worsening from the time that the first dose of study drug is administered until 30 days have elapsed following discontinuation of study drug administration.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

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, or a hospitalization for respite care.
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.

For serious adverse events with the outcome of death (including death related to disease progression), the date and cause of death will be recorded on the appropriate case report form.

6.1.1.3 Adverse Events Expected Due to Study Related Endpoints

6.1.1.3.1 Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease are also considered an expected outcome for this study and will not be reported as adverse events.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.03).[35] For all reported serious adverse events that increase in severity, the supplemental eCRFs also need to be updated to reflect the change in severity.

For AEs not captured by the NCI CTCAE Version 4.03, the following should be used:

Grade 1	The adverse event is transient and easily tolerated by the subject (mild).
Grade 2	The adverse event causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe).
Grade 4	The adverse event is life threatening requiring urgent intervention (severe).
Grade 5	The adverse event resulted in death of the subject (severe).

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the 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 a causality or deemed it not assessable, AbbVie will consider the event associated to study drug.

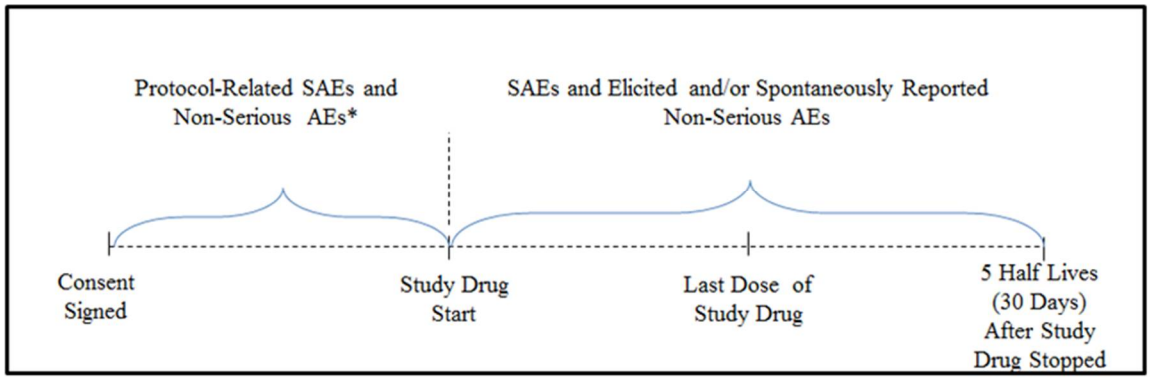
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an 'other' cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days, following discontinuation of navitoclax administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related serious adverse events and protocol-related non-serious adverse events will be collected from the time the subject signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



* Only if considered by the Investigator to be causally related to study-required procedures.

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Therapeutic Area Safety Team at:

TA Safety Team
1 North Waukegan Road
North Chicago, IL 60064

Safety Phone: +1 (833) 942-2226
Safety Email: SafetyManagement_TA@abbvie.com

For any subject safety concerns, please contact the TA MD/SD listed below:

Therapeutic Area Medical Directors

[redacted] MD, FACP
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
Telephone Contact Information:
Office : [redacted]
Mobile:
Email:

[redacted] MD, MS, MPH
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
Mobile: [redacted]
Email:

In emergency situations involving study subjects when the primary AbbVie TA MD/SD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD/SD:

Phone: +1 (973) 784-6402

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the

protocol and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines, and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness. For ruxolitinib, the reference document used for SUSAR reporting in the European Union countries will be the most current version of the Summary of Product Characteristics (SmPC).

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to an AbbVie representative (Section 6.1.5) within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

All subjects (females and males) should be informed that contraceptive measures (refer to Inclusion Criteria for the details on contraception) should be taken throughout the study and for at least 30 days for females and 90 days for males after the last dose of navitoclax and/or ruxolitinib. Male subjects should be informed that contraceptive measures should be taken by their female partner. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of a pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information, and the pregnancy will be followed to outcome.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management Guidelines

Navitoclax may be associated with cytopenias, notably thrombocytopenia, in patients based on observations made during previous clinical trials in other indications and preliminary safety data from Cohort 1a of this study.

The guidelines noted below should be implemented for all subjects unless previously discussed and approved with the AbbVie TA MD/SD (Section 6.1.5).

If a navitoclax interruption is necessary, navitoclax may be reintroduced at the same or lower dose based on the guidance below. If a dose reduction below 50 mg once daily is required, the dose of navitoclax may be reduced to 25 mg once daily following consultation with the AbbVie TA MD/SD.

The same navitoclax dose level shall not be attempted more than twice consecutively without prior approval from the AbbVie TA MD/SD.

The local approved ruxolitinib label should be referenced for guidance on ruxolitinib dose modifications for subjects with hepatic or renal impairment, drug-drug interactions, precautions, monitoring and management of hematologic and non-hematologic toxicities.

For subjects who require interruption of ruxolitinib per the label but are considered to be at increased risk for exacerbation of splenomegaly and clinically 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 or ruxolitinib (if applicable) dose level to be administered, for individual subjects will be medically managed by the Investigator in consultation with the AbbVie TA MD/SD (Section 6.1.5).

Intermediate dose levels (e.g., 150 mg once daily) may be administered at the discretion of the investigator. If intermediate dose levels are utilized prior to Week 24, consultation with the AbbVie TA MD/SD is required prior to implementation.

Decisions to delay or interrupt the study treatment for active COVID-19 infection should be made by the treating investigator after considering the subject's clinical assessment of the severity of infection, current status of MF and treatment tolerance, as well as the general medical condition. Treatment interruption longer than 28 days must be discussed with the TA MD/SD.

6.1.7.1 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 Appendix I, for appropriate dosing and management of all subjects for safety.

Any Grade ≥ 2 bleeding event (without regard to platelet count) will require interruption and possible discontinuation of dosing. Upon resolution of a Grade ≥ 2 bleeding event, study treatment may be reintroduced at the same or lower dose level, provided the patient is asymptomatic with no evidence of an active bleed.

The investigator should perform additional hematology labs on Day 3 and/or Day 4 for subjects with a lower baseline platelet count or for those that experience a 24-hour platelet count drop of > 40% from the pre-dose platelet count. Additional hematology labs should be performed based on the platelet counts as medically indicated at the discretion of the investigator.

If platelet transfusions are required in response to active bleeding, dosing of navitoclax 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 myelosuppression. 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 initial increase in platelet counts post-transfusion may be smaller and the duration of response may be shorter. For this reason, 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 monitoring of platelets should include:

- A platelet count obtained 10 – 60 minutes post-transfusion
- A platelet count obtained approximately 24 hours post-transfusion

6.1.7.2 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 found in Appendix I 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 Appendix I, 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 Appendix I, support with G-CSF and/or prophylaxis with antibiotics may be considered at the discretion of the investigator. If clinically necessary in the opinion of the investigator, ruxolitinib dosing, if applicable, may be considered for resumption prior to recovery of ANC >1.0 x 10^9/L.

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

6.1.7.3 Management of Infections

Subjects who develop clinically significant infections, including COVID-19, should have navitoclax held until infection resolves or is controlled. Subjects may restart navitoclax 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 carinii/jiroveci* pneumonia infections. Additionally, the potential for drug-drug interactions should be considered. In particular, there is a potential for significant drug-drug interactions when administering azole antifungal agents and caution should be taken when co-administered with navitoclax.

If study treatment is held in response to a confirmed (viral test positive) or suspected COVID-19 infection, study treatment may resume once the following COVID-19 viral clearance criteria are met:

- **Symptomatic subjects:**
  - At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- **Asymptomatic subjects:**
  - At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

6.1.7.4 Management of Other Toxicities

If other events occur that are related to navitoclax or ruxolitinib (if applicable), the investigator may delay and/or modify dosing of navitoclax and/or ruxolitinib as appropriate and clinically indicated.

Grade ≥ 3 non-hematologic toxicity (e.g., nausea, vomiting, and diarrhea when additional supportive care fails, neurotoxicity; increase in AST, ALT, bilirubin) that is related to navitoclax or ruxolitinib (if applicable) will require interruption and possible discontinuation of dosing if toxicity is not resolved. Study treatment may be reintroduced at the same or lower dose level if the toxicity returns to Grade ≤ 1 or to baseline if Grade 2 at study entry.

Similarly, during the navitoclax escalation period for Cohort 1a, navitoclax should be delayed for the occurrence of any Grade ≥ 3 non-hematologic toxicity related to navitoclax. Navitoclax may be reintroduced at the same or lower dose (in consultation with the AbbVie TA MD/SD) if the toxicity returns to Grade ≤ 1 or to baseline if Grade 2 at study entry.

All subjects should be monitored according to the schedule of assessments (Appendix C) for new-onset non-hematologic toxicity and renal toxicities, with dose delay or reduction as appropriate. For ruxolitinib, local, approved product label should be referenced for monitoring guidelines.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

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 (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form in EDC on the appropriate eCRF. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified,

including those that may be due to the COVID-19 pandemic) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:

[redacted]
8401 TransCanada Highway
Saint-Laurent, Quebec
H4S 1Z1 Canada

Office:
E-mail: [redacted]

Alternate Contact:

[redacted]
Mühlentalstrasse 36
CH-8200, Schaffhausen
Switzerland

Office:
E-mail: [redacted]

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Definition of Analysis Populations

Full Analysis Set (FAS) consists of all subjects who take at least one dose of navitoclax. The FAS will be used for efficacy and demographic analyses unless otherwise specified in the protocol or in the SAP (Statistical Analysis Plan).

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

Unless otherwise noted in the SAP, all analyses will be performed separately for 3 sets by study treatment:

- Set 1: This set consists subjects from Cohort 1a and 1b.

- Set 2: This set consists all subjects from Cohort 2.
- Set 3: This set consists all subjects from Cohort 3.

8.1.1 Baseline Characteristics

Unless otherwise stated, baseline for a given variable will be defined as the last non-missing value for that variable obtained prior to the first dose of any component of study drug.

Continuous demographic data (e.g., age, height, and weight) will be summarized with means, standard deviation, minimum, maximum, and range. Categorical data (e.g., sex, race, etc.) will be summarized with frequencies and percentages.

Frequencies and percentages will be computed for medical history parameters.

8.1.2 Pharmacokinetics

Plasma concentrations of navitoclax, potential navitoclax metabolite(s), and ruxolitinib and their available pharmacokinetic parameter values will be tabulated for each subject and by visit. Summary statistics will be computed for each sampling time and each parameter.

8.2 Efficacy Endpoints

8.2.1 Primary Efficacy Endpoint

The primary endpoint is at least 35% reduction from baseline in spleen volume at Week 24 (SVR_{35W24}) as measured by MRI/CT.

8.2.2 Secondary Efficacy Endpoints

The secondary endpoints are:

- At least 50% reduction in TSS at Week 24 from baseline as measured by MFSAF version 4.0

- The anemia response rate
- Change in the bone marrow fibrosis grade according to the European consensus grading system[35] (Appendix F)

8.2.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints may include, but are not limited to:

- At least 35% reduction in SVR_{35} from baseline as measured by MRI or CT scan, at any time point during study
- Duration of SVR_{35}
- At least 50% reduction in palpable splenomegaly from baseline per modified IWG criteria
- At least 50% reduction in TSS at any time point from baseline as measured by MFSAF v4.0
- Change from baseline in TSS
- Red blood cell transfusion during study treatment
- Duration of anemia response
- Exploratory analyses of the MFSAF v4.0, PROMIS Fatigue SF 7a, and EORTC QLQ-C30 Overall response
- PFS per modified IWG criteria
- OS

8.3 Statistical Analysis

Unless otherwise noted, all analyses are performed by study treatment for each cohort, no formal statistical test will be performed. Estimation approach will be used. Details on the analysis will be provided in the Statistical Analysis Plan (SAP).

8.3.1 Efficacy

SVR_{35w24} will be calculated as the proportion of subjects who achieve ≥ 35% reduction from baseline in spleen volume at Week 24 (SVR_{35w24}). The point estimates of SVR_{35w24}

will be provided. The exact 95% confidence intervals as derived by the Clopper-Pearson method will also be presented. In addition, absolute and percent change from baseline of spleen volume will be summarized with mean, standard deviation, median, minimum and maximum reported. TSS response (at least 50% reduction) rate will be calculated as the proportion of subjects who achieve at least 50% reduction in TSS at Week 24 from baseline. The point estimates of TSS response rate at Week 24 will be provided and corresponding exact 95% confidence intervals as derived by the Clopper-Pearson method will be presented.

Anemia response rate and corresponding exact 95% confidence intervals as derived by the Clopper-Pearson method will be presented.

Descriptive statistics for change in grades of bone marrow fibrosis will be reported.

8.3.2 Safety

The safety of navitoclax alone or in combination with navitoclax and ruxolitinib will be assessed by evaluating duration of exposure, adverse events, serious adverse events, deaths, and changes in laboratory determinations and vital sign parameters.

8.3.2.1 Duration of Exposure of Study Treatment

Duration of exposure of study treatment will be summarized for both navitoclax and ruxolitinib (when applicable), respectively, by the mean, standard deviation, median, min and max.

8.3.2.2 Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the first dose of day of the study drug. Analyses will not include those that have an onset greater than 30 days after the last dose of the study drug.

Treatment-emergent adverse events will be coded and summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities

(MedDRA) adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given severity, NCI CTCAE version 4.03 toxicity grade and relationship to study drug will be provided.

8.3.2.3 Serious Adverse Events

Serious adverse events will be summarized using the same methods as adverse events described in the previous section.

8.3.2.4 Deaths

The number of subject deaths will be summarized 1) for deaths occurring while the subject was still receiving study drug in this study, 2) for deaths occurring off treatment within 30 days after the last dose of study drug, and 3) for all deaths in this study regardless of the number of days after the last dose of study drug.

8.3.2.5 Laboratory Data

Where applicable, laboratory values will be categorized according to the NCI CTCAE version 4.03 grades, and shifts from baseline grade to post-baseline maximum grades will be assessed.

Detailed listings of data for subjects experiencing NCI CTCAE Grade 3 to 4, blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

8.3.2.6 Vital Signs

Detailed listings of data for subjects experiencing potentially clinically significant vital sign values according to the AbbVie-defined criteria for vital sign values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

8.4 Determination of Sample Size

Approximately 174 subjects in total will be enrolled in this study. Point estimate and exact 95% confidence interval of SVR_{35w24} rate corresponding to expected observed number of subjects with SVR_{35w24} are presented in Table 5.

Table 5. Point Estimates and 95% CI of Rate of SVR_{35w24} Corresponding to Observed Number of Subjects with SVR_{35w24}

Cohort	Sample size	Number of Subjects with SVR_{35w24}	Point Estimate (SVR_{35w24} Rate) (%)	Exact 95% CI		Half Width of CI
				Lower Limit (%)	Upper Limit (%)	
1a	34	16	47.06	29.78	64.87	17.55
1a	34	18	52.94	35.13	70.22	17.55
1a	34	20	58.82	40.70	75.35	17.33
1a	34	22	64.71	46.49	80.25	16.88
1b	70	32	45.71	33.74	58.06	12.16
1b	70	34	48.57	36.44	60.83	12.19
1b	70	36	51.43	39.17	63.56	12.19
1b	70	38	54.29	41.94	66.26	12.16
2 or 3	30	12	40.00	22.66	59.40	18.37
2 or 3	30	14	46.67	28.34	65.67	18.67
2 or 3	30	16	53.33	34.33	71.66	18.67
2 or 3	30	18	60.00	40.60	77.34	18.37

Based on the table above, this study with proposed sample sizes will provide a reasonable precise estimate of the proportion of subjects with SVR_{35w24} for each cohort. According to Section 8.1, Set 1 is expected to consist of subjects from Cohorts 1a and 1b. Also, if true probability of experiencing a serious adverse event (SAE) due to the study treatment is 10%, then the probability of observing at least one SAE in 34 subjects is more than 97% in Cohort 1a; the probability of observing at least one SAE in 80 subjects is more than 99% in Cohort 1b; the probability of observing at least one SAE in 30 subjects is more than 95% in Cohort 2 or 3, respectively. Therefore, from safety assessment prospective the proposed sample size is adequate.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (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 clinical investigator are specified in Appendix A.

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 TA MD/SD if any urgent safety measures are taken to protect the subjects against any immediate hazard.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related Screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Optional collection of blood samples to evaluate the potential drug-drug interactions between navitoclax and ruxolitinib for subjects in Cohort 1b (Appendix D) will only be collected if the subject has voluntarily signed and dated informed consent, approved by the IRB/IEC, after the nature of the testing has been explained and the subject has had an

opportunity to ask questions. The separate informed consent must be signed before the optional blood samples are collected. If the subject does not consent to the optional blood sample collection, it will not impact the subject's participation in the study.

Optional exploratory research sample collection and analysis will only be performed if the subject has voluntarily signed and dated informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate informed consent must be signed before the optional exploratory research samples are collected. If the subject does not consent to the optional exploratory research testing, it will not impact the subject's participation in the study.

In the event a subject withdraws consent, stored biomarker and exploratory research samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for future research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional temporary verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. An appropriately signed and dated informed consent form should be obtained from the subject afterwards, as soon as possible.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from

automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded to the appropriate source document. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data 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.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will

be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

Patient reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor Signant Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, Signant Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by Signant Health.

Internet access to the ePRO data will be provided by Signant Health for the duration of the study. This access will be available for the duration of the study to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's ePRO data. It will be possible for the investigator to make paper print-outs from that media.

The ePRO data will be collected by the following methods:

Diary Based

- MFSAF Version 4.0 will be collected electronically via a handheld device into which the patient will record the required pieces of information on a daily basis. The electronic device will be programmed to allow data entry for each day. All data entered on the device will be immediately stored to the device itself and manually/automatically uploaded to a central server administrated by Signant Health. The Investigator and delegated staff will be able to access all uploaded patient entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

11.0 Data Quality Assurance

Prior to enrolling any subject in the study, a Site Training Visit will be held with AbbVie personnel, the Investigator(s), and the study coordinators/project manager(s). This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, case report form completion and specimen collection methods.

The AbbVie monitor will monitor the study site throughout the study. Source document review will be made against entries on the electronic case report forms and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after the case report forms are retrieved, a review of the data will be conducted by a physician or representative at AbbVie.

All data hand-entered in the database will be verified at AbbVie. Any discrepancies will be reviewed against the hard-copy case report form and corrected on-line. After completion of the entry process, computer logic and manual checks will be created to identify such items as inconsistent study dates. Any necessary corrections will be made to the database via the appropriate change form/electronic CRF.

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

Routine hematology, serum chemistry and serology tests will be conducted using a certified clinical laboratory. Laboratory reference ranges will be obtained prior to the initiation of the study and updated as necessary throughout the course of the study. A review of all laboratory results will be conducted by the AbbVie monitor, the Investigator and other appropriate personnel from AbbVie.

12.0 Use of Information

All information concerning navitoclax processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of navitoclax. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site

with other study records under adequate security and restricted access, and will not be retrieved by AbbVie.

Any research that may be done using biomarker research and/or optional exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from research samples may be provided to investigators and used in scientific publications or presented at medical conventions. Research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in

accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit or date of last follow-up contact, whichever is later.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for navitoclax and I am familiar with the product labeling for ruxolitinib.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Phase 2 Open-Label Study Evaluating Tolerability and Efficacy of Navitoclax Alone or in Combination with Ruxolitinib in Subjects with Myelofibrosis (REFINE)
Protocol Date:	04 October 2021

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
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., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
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 investigation and all 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. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Statistics
		Statistical Sciences & Analytics
		Clinical Study Leadership
		Clinical Pharmacology and Pharmacometrics

Appendix C. Study Activities*

Table 6. Study Procedures – Navitoclax Alone or in Combination with Ruxolitinib

Period	Screening[a]	Treatment														Follow-Up		
Week	–4 to 0	0	0	1	2	3	4	6	8	12	16	20	24	Q12 Weeks	TCV	30-Day Safety	PT[b]	Survival
Study Day	Within 28 days	1	2	8	15	22	29	43	57	85	113	141	169					
Visit Window (days)	–28	NA	NA	± 1	± 1	± 1	± 1	± 1	± 1	± 2	± 2	± 2	± 3	± 4	NA	NA	± 7	± 14
Activity																		
LOCAL LABS, EXAMS & ASSESSMENTS																		
Informed Consent	X[c]																	
Medical/Oncology History Assessment	X	X[d]																
TB Testing[e]	X																	
AE/Concomitant Medication Assessment	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Transfusion history/status	X[f]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical Exam (including skin, liver and spleen assessment)[g]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[h]	X						X								X			

Table 6. Study Procedures – Navitoclax Alone or in Combination with Ruxolitinib (Continued)

Period	Screening[a]	Treatment													Follow-Up		
Week	–4 to 0	0	0	1	2	3	4	6	8	12	16	20	24	Q12 Weeks	TCV	30-Day Safety	PT[b]	Survival
Study Day	Within 28 days	1	2	8	15	22	29	43	57	85	113	141	169					
Visit Window (days)	–28	NA	NA	± 1	± 1	± 1	± 1	± 1	± 1	± 2	± 2	± 2	± 3	± 4	NA	NA	± 7	± 14
Activity																		
Vital Signs	X[i]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
MFSAF version 4.0[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]				
EORTC QLQ-C30[K]	X	X					X		X	X			X	X	X			
PROMIS Fatigue SF 7a[K]	X	X					X		X	X			X	X	X			
PGIC[K]							X		X	X			X	X	X			
Pregnancy Test[l]	Serum	X					X		X	X	X	X	X	X[l]	X			
Hematology[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X	X[n]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation	X																	
Lipid Parameters (fasting)	X									X								

Table 6. Study Procedures – Navitoclax Alone or in Combination with Ruxolitinib (Continued)

Period	Screening[a]	Treatment														Follow-Up		
Week	–4 to 0	0	0	1	2	3	4	6	8	12	16	20	24	Q12 Weeks	TCV	30-Day Safety	PT[b]	Survival
Study Day	Within 28 days	1	2	8	15	22	29	43	57	85	113	141	169					
Visit Window (days)	–28	NA	NA	± 1	± 1	± 1	± 1	± 1	± 1	± 2	± 2	± 2	± 3	± 4	NA	NA	± 7	± 14
Activity																		
Bone Marrow Biopsy and Aspirate[w]	X									X			X	X[w]	X[x]		X[y]	
Cytogenetic Sampling[w,z]	X									X			X	X[w]	X[x]			
Disease Response Assessment										X			X	X[ff]	X		X[y]	
Imaging for spleen assessment[ee]	X									X			X	X[ee]	X[x]		X[y]	
Survival Assessments																		X[gg]
CENTRAL LABS																		
Blood for Plasma[o]	X			X	X	X	X		X	X			X	X[p]	X			
Blood for Allelic Burden[o]	X						X[q]		X[q]	X[r]			X	X[s]	X			

Table 6. Study Procedures – Navitoclax Alone or in Combination with Ruxolitinib (Continued)

Period	Screening[a]	Treatment														Follow-Up		
Week	**–4 to 0**	**0**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**Q12 Weeks**	**TCV**	**30-Day Safety**	**PT[b]**	**Survival**
Study Day	**Within 28 days**	**1**	**2**	**8**	**15**	**22**	**29**	**43**	**57**	**85**	**113**	**141**	**169**					
Visit Window (days)	**–28**	**NA**	**NA**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 3**	**± 4**	**NA**	**NA**	**± 7**	**± 14**
Activity																		
Blood for Mutational Profiling[o]	X						X[q]		X[q]	X[r]			X	X[t]	X			
Blood for Flow Cytometry[o]		X											X	X[u]				
Blood for Viable PBMC[o]		X											X	X[u]				
Blood for Translational Research-Heparin[o]	X												X	X[v]	X			
Blood for Translational Research- ACD (female/US only)[n]	X[hh]												X	X[u,v]				
Optional PG Blood Sample[o]	X									X					X			

Table 6. Study Procedures – Navitoclax Alone or in Combination with Ruxolitinib (Continued)

Period	Screening[a]	Treatment														Follow-Up		
Week	–4 to 0	0	0	1	2	3	4	6	8	12	16	20	24	Q12 Weeks	TCV	30-Day Safety	PT[b]	Survival
Study Day	Within 28 days	1	2	8	15	22	29	43	57	85	113	141	169					
Visit Window (days)	–28	NA	NA	± 1	± 1	± 1	± 1	± 1	± 1	± 2	± 2	± 2	± 3	± 4	NA	NA	± 7	± 14
Activity																		
Bone Marrow Aspirate for mutational profiling[o,aa]	X									X			X	X[o,w]	X[x]			
Bone Marrow Aspirate for Translational research[o,aa]	X														X[x]			
Bone Marrow Core Biopsy – IHC and Translational Research[o,aa]	X									X			X	X[o,w]	X[x]			
Pharmacokinetic Assessments for Navitoclax and Ruxolitinib[bb]	X[cc]	X	X	X[cc,dd]	X		X		X	X			X					

Table 6. Study Procedures – Navitoclax Alone or in Combination with Ruxolitinib (Continued)

Period	Screening[a]	Treatment														Follow-Up		
Week	–4 to 0	0	0	1	2	3	4	6	8	12	16	20	24	Q12 Weeks	TCV	30-Day Safety	PT[b]	Survival
Study Day	Within 28 days	1	2	8	15	22	29	43	57	85	113	141	169					
Visit Window (days)	–28	NA	NA	± 1	± 1	± 1	± 1	± 1	± 1	± 2	± 2	± 2	± 3	± 4	NA	NA	± 7	± 14
Activity																		
TREATMENT																		
Contact IRT for Screening/ enrollment	X	X																
Dispense and administration of study treatment		X		X	X	X	X	X	X	X	X	X	X	X				
Drug accountability assessment and compliance				X	X	X	X	X	X	X	X	X	X	X	X			

TCV = Treatment Completion Visit; PT = Post Treatment; D = Day

* Shows the required activities the subject encounters. The individual activities are described in detail and allowed modifications due to COVID-19 are detailed within Section 5.3.1.1.

a. Screening procedures must be performed within 28 days prior to initial study drug administration. The 28 day Screening window starts with the signing of the Informed Consent Form.

b. Post-Treatment visits will be performed every 12 weeks (± 1 week) until the subject has documented disease progression, initiation of post-treatment cancer therapy, or subject refusal of post-treatment follow-up visits.

Table 6. Study Procedures – Navitoclax Alone or in Combination with Ruxolitinib (Continued)

c. The informed consent must be obtained prior to performing any Screening or study-specific procedures.

d. On Day 1, additional medical history that is observed after signing of the informed consent but prior to initial study drug administration and not considered related to study-required procedures will be recorded in the subject's medical history.

e. Subjects to be enrolled in Cohorts 1b and 3 (not applicable for Cohort 1a as it is fully enrolled or Cohort 2, navitoclax monotherapy) will be assessed for evidence of increased risk for TB and tested for TB infection, per local guidelines, prior to Day 1. If TB Skin Test is utilized, it should be read by a licensed healthcare professional between 48 and 72 hours after administration. TB testing may be performed centrally if unable to be performed locally, however, a negative result must be confirmed prior to first dose.

f. Transfusion must be recorded during the time period of a minimum of 12 weeks before the start of study treatment.

g. A complete physical exam will be performed at Screening and TCV. A symptom-directed physical exam may be performed at other study visits at the discretion of the investigator. At a minimum, Spleen and liver palpation and measurement is required, plus skin exam is required for subjects in all Cohorts.

h. Additional ECGs may be performed as clinically necessary per the discretion of the investigator.

i. Height will be measured only at Screening.

j. MFSAF version 4.0 diary will be performed daily beginning at screening visit, pre-dose on Day 1 through Week 36 visit. For subjects enrolled in Cohorts 1b and 3 the screening period should be long enough to ensure at least 7 days to collect the daily MFSAF version 4.0 prior to Day 1.

k. EORTC QLQ-C30 version 3, PROMIS Fatigue SF 7a and PGIC should be completed prior to any other clinical assessments and prior to dosing.

l. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine or serum pregnancy test at Study Day 1. Negative pregnancy test must be available prior to first dose. Where required by local regulatory authority, urine pregnancy tests will be performed for females of childbearing potential every 4 weeks after Week 24 through treatment completion.

m. Hematology will be collected pre-dose and 4 hours after the first dose of navitoclax on Day 1; 24-hours post-first-dose on Day 2; additional timepoints indicated above in Table 6; and prior to navitoclax dose increases, reductions (if during a clinic visit), or re-initiation after interruption. Additional monitoring may also be required as per Section 6.1.7.1 and Section 6.1.7.2.

n. Chemistry will be collected pre-dose on Day 1 Week 0

o. Refer to Section 5.3.1.3 for sample matrix requirements for biomarker and optional exploratory research samples.

p. Collected at Week 48 (D337) and Week 96 (D673).

q. Cohort 1a only.

r. Cohorts 1a and 3 only.

Table 6. Study Procedures – Navitoclax Alone or in Combination with Ruxolitinib (Continued)

s. Collected at Week 36 (D253), 48(D337), 60 (D421), 72 (D505), and 96 (D673).

t. Collected Weeks 48 (D337), 72 (D505), and 96 (D673) for Cohorts 1b and 2, and Weeks 48 (D337), 72 (D505), 96 (D673), 120 (D841), and 144 (D1009) for Cohort 3.

u. Collected Week 48 (D337) for Cohorts 1b, 2 and 3.

v. Collected Week 96 (D673) for Cohorts 1b, 2, and 3.

w. For visits with bone marrow sampling, hematology and chemistry labs should be performed on the same day as the bone marrow assessment. Bone marrow biopsy and aspirate as well as cytogenetics will be performed at Screening (results from historical bone marrow samples will not be accepted), Weeks 12 (D85), 24 (D169), 48 (D337) and 96 (D673). All bone marrow sampling must be completed within the ± 7 day window for the study visit. Additional bone marrow sampling and cytogenetics should be performed if disease progression is suspected, at the discretion of the investigator.

x. Procedure should be performed if the subject discontinues from the study for a reason other than documented disease progression and if this procedure has not been done within the last 12 weeks.

y. MRI (CT allowed if MRI is medically contraindicated), Bone Marrow sampling and Disease Response Assessments to be performed during Post-Treatment FU visits as necessary if disease progression is suspected.

z. May be obtained from bone marrow or peripheral blood sampling.

aa. Bone marrow biopsy/aspirate samples for exploratory biomarker analysis should be split from the samples collected for local clinical assessment. All bone marrow sampling must be completed within the ± 7 day window for the study visit.

bb. See Table 7 and Appendix D for the schedule of Pharmacokinetic Assessments for Navitoclax and Ruxolitinib.

cc. Cohort 1b-DDI only. See Appendix D Table 8.

dd. Cohort 1b-DDI only for Days 7 and 8. See Appendix D Table 8.

ee. MRI/CT of the abdomen to determine spleen volume will be conducted at Screening, Weeks 12 (D85), 24 (D169), 36 (D253), 48 (D337), 72 (D505) and 96 (D673). Additional MRI/CT should be performed if disease progression is suspected, at the discretion of the investigator. All MRI/CT assessments must be completed within the ± 7 day window for the study visit. All MRI/CT must be sent to a central imaging vendor.

Table 6. Study Procedures – Navitoclax Alone or in Combination with Ruxolitinib (Continued)

ff. Disease Response Assessment to be performed at Weeks 12 (D85), 24 (D169), 36 (D253) 48 (D337), 72 (D505) and 96 (D673). For disease assessments performed at Week 36 and 72, a repeat bone marrow biopsy is not required unless disease progression is suspected. The prior bone marrow assessment may be used for the purposes of assessing disease response per modified IWG criteria.

gg. Survival information (e.g., date and cause of death, post-treatment cancer therapies including systemic therapy, radiation therapy, cancer related-procedures and stem-cell transplant, response to post-treatment cancer therapies) will be collected via telephone calls (e.g., to subject or family member), clinic visits, and/or public database searched every 6 months (± 2 weeks) after the last study visit up to 5 years after TCV (provided informed consent has not been withdrawn for collection of such information).

hh. Sample may be collected at Screening or Week 0 Day 1.

Table 7. Schedule of Pharmacokinetic Assessments for Navitoclax and Ruxolitinib

Cohort	Visit Schedule	Before Drug Administration	After Drug Administration[a]	Sampling Plan Specimen Matrix
1a	Day 1	Predose	2h, 4h, 6h, 8h	Blood → Plasma Frozen –20°C or colder
	Day 2	Predose[b]		
	Day 8 Day 15 Day 22 Day 29 Day 43 Week 8 (Day 57) Week 12 (Day 85) Week 24 (Day 169) Week 48 (Day 337)	Predose		
1b, 2[c], 3	Day 1	Predose	Cohort 1b and 3: 4h Cohort 2: 2h, 4h, 6h, 8h	
	Day 2	Predose[b]		
	Day 15 Day 29 Week 8 (Day 57), Week 12 (Day 85), Week 24 (Day 169)	Predose		

h = hours; min = minute

On days when PK samples are collected pre-dose, navitoclax (all cohorts) and ruxolitinib (Cohort 1a, 1b, and 3) should be taken at the same time during the clinic visit following the blood sample collection.

The date and time of each PK sample collection and the date and time of the last two doses of navitoclax and/or ruxolitinib at each visit will be captured on the eCRF.

a. Samples for 2h and 4h should be collected within 10% of the scheduled time; Samples for 6h and 8h should be collected with ± 30 min.

Table 7. Schedule of Pharmacokinetic Assessments for Navitoclax and Ruxolitinib (Continued)

b. Collection is 24 hours (± 30 min) post-first dose of navitoclax on Day 1 and before dosing of navitoclax and morning dose of ruxolitinib (if applicable, e.g., Cohorts 1a, 1b and 3) on Day 2.

c. Sampling schedule is for navitoclax only.

Appendix D. Evaluation of Potential Drug-Drug Interaction between Navitoclax and Ruxolitinib

A total of approximately 10 subjects from Cohort 1b on a stable dose of ruxolitinib with a baseline platelet count > 150×10^9/L at the time of screening will participate in the drug-drug interaction (DDI) sub-study following informed consent for the collection of additional blood samples.

Navitoclax will be administered at a starting dose of 200 mg once daily beginning on Day 1. Pharmacokinetics (PK) of ruxolitinib when administered alone on Day 0 will be compared with its PK when co-administered with navitoclax on Day 7. Subjects must have received a stable dose of navitoclax for at least 4 days before the PK sample collection on Day 7. If navitoclax dose de-escalation has occurred before Day 7, PK samples may be taken at a future visit, provided subject has received a stable dose of navitoclax for at least 4 days. Pharmacokinetic samples will be collected prior to dosing and at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours after dosing on Day 0 (ruxolitinib without navitoclax) and Day 7 (ruxolitinib with navitoclax). Pharmacokinetic schedule for the subgroup of subjects participating in DDI evaluation in Cohort 1b is presented in Table 8.

Data from at least 8 subjects receiving navitoclax at the 200 mg dose level and with PK samples collected on at least Days 0 and 7 will be required.

Table 8. Complete Schedule of Pharmacokinetic Assessments for Navitoclax and Ruxolitinib in a Subgroup (n ~10) of Cohort 1b Subjects for DDI Assessment (DDI cohort is applicable to subjects who sign a separate informed consent)

Drug	Visit Schedule	Before Drug Administration	After Drug Administration[a]	Sampling Plan Specimen Matrix
Ruxolitinib Only	Day 0	Predose	0.25h, 0.5h, 1h, 2h, 4h, 6h, 8h	Blood → Plasma Frozen –20°C or colder
Ruxolitinib + Navitoclax	Day 1	Predose[b]	4h	
	Day 2	Predose[c]		
	Day 7	Predose[d]	0.25h,[d] 0.5h,[d] 1h,[d] 2h,[d] 4h,[d] 6h,[d] 8h[d]	
	Day 8	Predose[c]		
	Day 15 Day 29 Week 8 (Day 57) Week 12 (Day 85) Week 24 (Day 169)	Predose		

h = hours; min = minute

The date and time of each PK sample collection and the date and time of the last two doses of navitoclax and/or ruxolitinib at each visit will be captured on the eCRF.

a. Samples for 0.25h and 0.5h should be collected with ± 5 min of the scheduled time. Samples for 1h, 2h and 4h should be collected within 10% of the scheduled time; Samples for 6h and 8h should be collected with ± 30 min.

b. Before dosing of navitoclax and morning dose of ruxolitinib on Day 1.

c. Collection is 24 hours (± 30 min) post dose of navitoclax on prior day and before dosing of navitoclax and morning dose of ruxolitinib.

d. Subjects must have received a stable dose of navitoclax for at least 4 days immediately prior Day 7 before PK the sampling collection on Day 7. If not, PK samples may be taken at a future visit, provided subject has received a stable dose of navitoclax for at least 4 days.

Appendix E. Modified IWG-MRT/ELN Response Criteria for Myelofibrosis

Table 9. Summary of Response Criteria

Response Category	Response Requirements (for all response categories, benefit must last for ≥ 12 wk to qualify as a response)		
	Bone Marrow	**Peripheral Blood**	**Clinical**
Complete Remission (CR)	• Age-adjusted normocellularity • < 5% blasts • Grade ≤ 1 MF (Appendix F)	• Hgb ≥ 10g/dL • Neutrophils ≥ 1×10^9/L • Platelets ≥ 100×10^9/L • < 2% immature myeloid cells	• Resolution of disease symptoms • Spleen/Liver not palpable • No evidence of EMH
Partial Remission (PR)	Not Applicable	• Hgb ≥ 10 g/dL • Neutrophils ≥ 1×10^9/L • Platelets ≥ 100×10^9/L • < 2% immature myeloid cells	• Resolution of disease symptoms • Spleen/Liver not palpable • No evidence of EMH
	OR		
	• Age-adjusted normocellularity • < 5% blasts • Grade ≤ 1 MF (Appendix F)	• Hgb ≥ 8.5 g/dL • Neutrophils ≥ 1×10^9/L • Platelets ≥ 50×10^9/L • < 2% immature myeloid cells	• Resolution of disease symptoms • Spleen/Liver not palpable • No evidence of EMH
Clinical Improvement	The achievement of anemia, spleen or symptom response without progressive disease or increase in severity of anemia, thrombocytopenia or neutropenia*		
Anemia Response	Transfusion-independent (baseline Hgb < 10 g/dL): Hgb increase ≥ 2 g/dL Transfusion dependent: becoming transfusion independent**		
Spleen Response	A baseline splenomegaly that is palpable at 5 – 10 cm below the LCM, becomes not palpable*** A baseline splenomegaly that is palpable at > 10 cm below the LCM, decreases by ≥ 50%*** MRI/CT showing ≥ 35% SVR		
Symptoms Response	≥ 50% reduction in MF-SAF TSS		
Stable Disease	Belonging to none of the above response categories		

EMH = extramedullary hematopoiesis; LCM = left costal margin

* Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥ 2 g/dL decrease in Hgb from pretreatment baseline that lasts for ≥ 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or ANC. In addition, assignment to Clinical Improvement requires a minimum platelet count of ≥ 25×10^9/L and ANC ≥ 0.5×10^9/L.

** Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase.

*** Requires confirmation by MRI/CT with a ≥ 35% SVR.

Table 10. Summary of Cytogenetic Remission

Cytogenetic Remission Category	Cytogenetic Remission Requirements At least 10 metaphases must be analyzed Requires confirmation by repeat testing within 6 months
Complete Cytogenetic Remission	Eradication of a preexisting abnormality
Partial Cytogenetic Remission	≥ 50% reduction in abnormal metaphases (to qualify for PR: must have ≥ 10 abnormal metaphases at baseline)

Table 11. Summary of Molecular Remission

Molecular Remission Category	Molecular Remission Requirements Must be analyzed in peripheral blood granulocytes Requires confirmation by repeat testing within 6 months
Complete Molecular Remission	Eradication of a pre-existing abnormality
Partial Molecular Remission	≥ 50% decrease in allele burden (to qualify for PR: must have ≥ 20% mutant allele burden at baseline)

Table 12. Summary of Progression/Relapse Criteria

Progression/Relapse Category	Progression/Relapse Criteria
Progressive Disease	At least 1 of the following: • Appearance of a new splenomegaly that is palpable at least 5 cm below the left costal margin (LCM)* • A ≥ 100% increase in palpable distance below LCM, for baseline splenomegaly of 5 – 10 cm* • A 50% increase in palpable distance below LCM, for baseline splenomegaly of > 10 cm* • MRI/CT showing a ≥ 25% increase in spleen volume from baseline • Leukemic transformation confirmed by a bone marrow blast count of ≥ 20% • A peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1×10^9/L that lasts for at least 2 weeks
Relapse	At least 1 of the following: • No longer meeting criteria for at least Clinical Improvement after achieving Complete Response, Partial Response or Clinical Improvement • Loss of anemia response persisting for ≥ 1 month • Loss of spleen response persisting for ≥ 1 month
Cytogenetic/Molecular Relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

LCM = left costal margin

* Requires confirmation by MRI/CT with a ≥ 25% increase in spleen volume from baseline.

Appendix F. Bone Marrow: Grading of Myelofibrosis

Table 13. Consensus on Grading of MF

Grading	Description
MF-0	Scattered linear reticulin with no intersections (cross-overs) corresponding to normal bone marrow
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
MF-3	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

Notes: Thiele J 2005.[36]

Fiber density should be assessed in hematopoietic (cellular) areas.

Appendix G. Dynamic International Prognostic Scoring System (DIPSS)

Table 14. Dynamic International Prognostic Scoring System (DIPSS)

	Points		
Prognostic Variable	**0**	**1**	**2**
Age, years	≤ 65	> 65	
White blood cell count, × 10^9/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		

* To report constitutional symptoms as Yes, need presence of at least one of the 3 symptoms: weight loss, fever, or night sweats.

Notes: Passamonti F, 2010.[25]

Table 15. Dynamic International Prognostic Scoring System (DIPSS)-PLUS

Prognostic Variable	**Points**			
	0	**1**	**2**	**3**
DIPSS Risk Score	Low-risk	Int-1	Int-2	High-risk
Platelet Count		< 100 × 10^9/L		
Transfusion Need, Y/N	N	Y		
Unfavorable karyotype,[a] Y/N	N	Y		
Risk Group	**Points**			
Low	**0**			
Intermediate-1 (INT-1)	**1**			
Intermediate-2 (INT-2)	**2 or 3**			
High	**4 to 6**			

a. Unfavorable karyotype: complex karyotype defined as 3 or more abnormalities OR sole or two abnormalities that includes trisomy 8, 7/7q-, i(17q), 5/5q-. 12p-, inv(3), or 11q23 rearrangement.

Notes: Gangat N, 2011.[26]

Appendix H. Sample List of Excluded and Cautionary Medications

Anticoagulation Therapy (Excluded)	**Anti-Platelet (Excluded)**
coumadin (Warfarin)[a] and coumarin derivatives e.g., phenprocoumon	acetylsalicylic acid (Aspirin) (> 100 mg qd)
fondaparinux (Arixtra)	aspirin/extended-release dipyridamole (Aggrenox)
heparin[b]	clopidogrel (Plavix)
melagatran/ximelagatran	dipyridamole (Persantine)
rivaroxaban (Xarelto)	ticlopidine (Ticlid)
apixaban (Eliquis)	tirofiban (Aggrastat)
Strong CYP3A Inhibitors[c] (Cautionary; Excluded for Cohort 1b DDI sub-study)	
boceprevir	nefazodone
clarithromycin	nelfinavir paritaprevir/ritonavir
cobicistat	posaconazole
conivaptan	ritonavir
danoprevir/ritonavir	saquinavir
elvitegravir/ritonavir	telaprevir
idelalisib	telithromycin
indinavir	tipranavir/ritonavir
itraconazole	troleandomycin
ketoconazole	voriconazole
lopinavir/ritonavir	
mibefradil	
Anticoagulation Therapy (Cautionary)	**SSRIs and SNRIs (Cautionary)**
dalteparin (Fragmin)	citalopram (Celexa)
Enoxaparin (Lovenox) and other LMWH	escitalopram (Lexapro)
Tinzaparin (Innohep)	fluoxetine (Prozac)
	sertraline (Zoloft)
	duloxetine (Cymbalta)
	vortioxetine (Trintellix)
	venlafaxine (Effexor)
	desvenlafaxine (Pristiq)

NSAIDS[a] (Cautionary)	**CYP2C9 Substrates[c] (Cautionary)**
Aspirin > 100 mg daily	fluvastatin
Diclofenac	glipizide
Diflunisal	irbesartan
Etodolac	losartan
Ibuprofen	phenytoin
Indomethacin	sulfamethoxazole
Ketoprofen	sulfinpyrazone
Nabumetone	tolbutamide
Naproxen	torsemide
Oxaprozin	
Salsalate	
Sulindac	
Tolmetin	
Strong CYP3A Inducers[c] (Cautionary)	**CYP2C8 Substrates[c, d](Cautionary)**
apalutamide	amiodarone
avasimibe	amodiaquine
carbamazepine (Tegretol®)	cerivastatin
enzalutamine	chloroquine
mitotane	lovastatin[e]
phenytoin (Dilantin®)	paclitaxel (Taxol)
rifampin (Rifadin®)	pioglitazone
St. John's wort	repaglinide
	rosiglitazone
	simvastatin (Zocor)[e]
	troglitazone
P-gp Substrates (Cautionary)[c]	**BCRP Substrates (Cautionary)[c]**
dabigatran etexilate	rosuvastatin
digoxin	sulfasalazine
fexofenadine	

P-gp Inhibitors (Cautionary)[c]	BCRP Inhibitors (Cautionary)[c]
amiodarone	curcumin
carvedilol	cyclosporine A
clarithromycin	eltrombopag
dronedarone	
itraconazole	
lapatinib	
lopinavir and ritonavir	
propafenone	
quinidine	
ranolazine	
ritonavir	
saquinavir	
ritonavir	
telaprevir	
tipranavir	
ritonavir	
verapamil	
P-gp Inducers (Cautionary)[f]	**BCRP Inducers (Cautionary)[g]**
rifampin	efavirenz
phenytoin	rifampin
carbamazepine	phenytoin
St John's wort	quercetin
quercetin	curcumin
curcumin	omeprazole
	imatinib

a. Warfarin and certain NSAIDS are also CYP2C9 substrates. NSAIDS are allowed for limited duration only if platelets >100 x 10^9/L.

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

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

d Only certain statins qualify as CYP2C8 substrates.

e. Significant increase in AUC by co-administration of gemfibrozile, a potent CYP2C8 inhibitor. However, the involvement of CYP2C8 is unclear.

f. This is not an exhaustive list. Elmeliegy M, Vourvahis M, Guo C, et al. Clin Pharmacokinet. 2020;59(6):699-714.

g. This is not an exhaustive list. Gameiro M, Silva R, Rocha-Pereira C, et al. Molecules. 2017;22(4):600.

Refer to drug labels as needed for more information.

Appendix I. Dose Adjustment Guidelines for Thrombocytopenia and Neutropenia

- **After navitoclax 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, recheck platelets approximately every 2 to 3 days until recovery of platelets to ≥ 50 × 10^9/L.**
- **Navitoclax Dose levels for daily dosing: 200 mg, 150 mg, 100 mg, 75 mg or 50 mg**

Hematology Results	Action For Navitoclax	Navitoclax (All Cohorts)	Ruxolitinib Per Approved Local Label (Cohorts 1a, 1b, and 3)
Dose Modification for Thrombocytopenia			
Platelet counts ≥ 75 × 10^9/L	No change OR Increase dose	• Maintain current dose if platelet count ≤ 100× 10^9/L • Dose may be increased to 150 mg if the current dose of navitoclax is 100 mg and administered for at least 7 days and platelets have increased to > 100 × 10^9/L. • Dose may be increased to 200 mg if the current dose of navitoclax is 150 mg and administered for at least 7 days and platelets have increased to > 150 × 10^9/L.	• Reduce dose if current dose > 10 mg twice daily • Maintain current dose if receiving 10 mg twice daily • Dose may be increased to the label recommended dose if the current dose is lower than the label recommended dose and current dose of ruxolitinib has been administered for at least 7 days and platelet counts have remained stable at > 125 × 10^9/L with no other dose modifications of the regimen
Platelet counts ≥ 50 × 10^9/L to < 75 × 10^9/L	Dose reduction OR No Change	• Reduce navitoclax dose if platelets do not return to ≥ 75 × 10^9/L OR • Maintain current dose if counts are stable and no risk for bleeding per investigator discretion	• Consider dose reduction.

• **After navitoclax 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, recheck platelets approximately every 2 to 3 days until recovery of platelets to ≥ 50 × 10^9/L.** • **Navitoclax Dose levels for daily dosing: 200 mg, 150 mg, 100 mg, 75 mg or 50 mg**			
Hematology Results	**Action For Navitoclax**	**Navitoclax (All Cohorts)**	**Ruxolitinib Per Approved Local Label (Cohorts 1a, 1b, and 3)**
Dose Modification for Thrombocytopenia			
Platelet counts **< 50 × 10^9/L**	Dose interruption	• 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. • Resume per local approved label guidance 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**	Dose interruption	• Monitor hematology labs at least weekly until ANC ≥ 1.0 × 10^9/L • Resume at one dose level lower once ANC recover ≥ 1.0 × 10^9/L	• Maintain current dose or interrupt if at risk for infection per investigator discretion.
Absolute neutrophil count (ANC) **< 0.5 × 10^9/L**	Dose interruption	• Monitor hematology labs at least weekly or often as needed until ANC ≥ 1.0 × 10^9/L. • Resume at one dose level lower once ANC recover ≥ 1.0× 10^9/L	• May interrupt per local label. May taper if high risk for exacerbation in discussion with TA MD. • Resume at same or lower dose.