TITLE PAGE

Protocol Title:

A Phase 2b, Open-label, Multicenter, Randomized, Controlled, 2-Arm Study to Assess the Efficacy and Safety of Orally Administered NS-018 versus Best Available Therapy in Subjects with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis with Severe Thrombocytopenia (Platelet Count <50,000/μL)

Protocol Number: NS-018-201

Amendment Number: Protocol Version 3.0

Product: NS-018 (Ilginatinib)

Study Phase: Phase 2b

Sponsor Name:

NS Pharma, Inc.
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Regulatory Agency Identifying Number(s):

IND #: 109286
EudraCT #: 2021-000369-34
EU CT #: 2023-504462-39-00

Date of Protocol: 07 August 2023

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

[redacted]

11-Aug-2023 | 3:29:01 PM EDT

Date

Vice President, Research and Development
NS Pharma, Inc.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY				
Document	**Date**	**Amendment No.**	**Substantial**	**Region**
Version 3.0	07 August 2023	2	Yes	Europe, North America, Turkey, Poland, and Asia
Version 2.0	15 September 2022	1	Yes	Poland, Turkey, North America, and Asia
Original Protocol	13 October 2021	-	-	Europe, North America, and Asia.

Amendment Protocol Global Version 3.0 (07 August 2023)

Overall Rationale for the Global Amendment:

The purpose of this global amendment from Protocol Version 2.0 is to harmonize the protocol language related to contraception per Clinical Trials Facilitation Group (CTFG) guidance and is aligned to harmonize with the European union (EU) submissions. Changes that apply to all countries are harmonized throughout this amendment where applicable. This global protocol amendment consolidates country-specific protocol changes requested by each country's competent authority.

The changes from Protocol Version 2.0 to this amendment are provided in the following table.

Section # and Name	Description of Change	Brief Rationale
Throughout	Updated Version 2.0 to Version 3.0, updated abbreviations, Appendix numbering, minor wording changes, and formatting as needed. Changed ilginatinib to NS-018 Changed 'no therapy' to 'supportive care/therapy'	Changes required amendment with new version number and updates to text, appendices, formatting, drug name, etc.
Title Page	EU CT number added: 2023-504462-39-00.	EU CT number required.
1.1 Synopsis, Best Available Therapy Dosage 4.1 Overall Design, Best Available Therapy Dosage	Added that the Investigator will decide the BAT that will be administered during the screening period and BAT must include one of the following; hydroxyurea, danazol, fedratinib, ruxolitinib, interferon, corticoid, erythropoietin, purinethol, thalidomide, lenalidomide or 'supportive care/therapy'.	Clarification and BAT 'no therapy' replaced with BAT specific medication or 'supportive care/therapy' to clarify that subjects are receiving other types of treatment for myelofibrosis. Added the list of BATs to meet the requirement of the new Clinical Trial Registration in EU.
	Added clarification that 'supportive care/therapy' refers to blood products fluids (crystalloids), pain medications, and/or antibiotics, that subjects will need to manage myelofibrosis symptoms and complications.	Clarification.
	Clarified that the dose and schedule for BAT will be decided by Investigator based on subject condition and according to manufacturer's instruction or Investigator discretion.	Clarification.

Section # and Name	Description of Change	Brief Rationale
	Added that subjects whose standard of care treatment is JAK inhibitor will be allowed in BAT group or as BAT.	Clarification.
	Removed pacritinib, ruxolitinib, or fedratinib may be administered as a standard of care/BAT.	Clarification.
	Modified text JAK inhibitor can be allowed as BAT if the JAK inhibitor was administered as a standard of care and that BAT may be changed at any time during the randomization period per the Investigator's assessment.	Clarification.
1.1 Synopsis, Study Visits 1.3 Global Schedule of Assessments 4.1 Overall Design, Study Visits 8.0 Study Assessments and Procedures 8.2.4 Clinical Safety Laboratory Assessments Appendix 15 Schedule of Assessment for South Korea Only Appendix 16 Schedule of Assessments for UK Only Appendix 17 Schedule of Assessments for Germany Only	Clarified safety laboratory assessments for each cycle and when a central laboratory can be used.	Text was updated, as NS-018 has very limited clinical data to date, and an adjustment of the test plan to closely monitor safety of BAT subjects transitioning to NS-018 was required. This change is to clarify the schedule of safety laboratory assessments during the randomized period and after transition from BAT to NS-018 for all subjects.
	Added safety laboratory assessments that will be collected for South Korea only for the subjects transitioning from BAT to NS-018.	Added at the request of Korea regulatory authority.
	Clarified when physical examinations, vital signs, and ECGs will be collected for each cycle.	Clarification.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Study Visits 4.1 Overall Design, Study Visits	"JAK-inhibitor" was replaced with "ruxolitinib" while clarifying the washout period before starting NS-018 at Cycle 1 and Cycle 7.	Clarification.
	Added taper off or washout requirement for subjects transitioning from BAT to NS-018.	Clarification.
1.1 Synopsis, Study Visits 4.1 Overall Design, Study Visits	Added that changes in MF-directed treatment should be documented.	Clarification.
1.1 Synopsis 1.2 Schema 1.3 Global Schedule of Assessments 4.1 Overall Design 8.0 Study Assessments and Procedures	Added cross reference to SoAs for South Korea, UK, and Germany for study visits and assessments.	Provide SoAs for study assessments specific to each country.
1.1 Synopsis, Number of Investigators and Study Centers	Added additional study centers may be added.	Text was added to support enrollment.
1.2 Schema	Revised footnote a to include subjects in the control group may receive BAT according to the Investigator's discretionand based on the subject's condition.	Clarification.
	Revised footnote b to include BAT 'supportive care/therapy'.	Clarification.

Section # and Name	Description of Change	Brief Rationale
	Revised the Additional Assessment Guidance table after the Study Schema. • Added ECG details for UK only. • Removed MF-SAF, PROMIS, and EQ-5D-5L from the table. • Added safety laboratory assessments and timing for South Korea only.	Clarification.
1.3 Global Schedule of Assessments	Modified the Visit Windows from plus/minus to only plus 3 days.	Clarification.
	Modified the bone marrow assessment at Cycle ≥ 7 to update from Cycles 7 to Cycle 13.	Clarification.
	Added therapies/procedures to Concomitant medication assessment.	Clarification.
	Modified footnote b from 10 days to 14 days for spleen measurement.	Clarification.
	Added to footnote f clarification on safety laboratory assessments for subject transitions from BAT to NS-018. Added direct bilirubin for screening. Clarified total bilirubin for safety assessment.	Clarification.
	Added footnote g to 12-lead ECG assessments in the table where appropriate.	Clarification.
	Added to footnote g the collection of ECGs at each Cycle and Day.	Clarification.

Section # and Name	Description of Change	Brief Rationale
	Modified footnote h from 3 months to 6 months.	Baseline bone marrow assessment was changed from 3 to 6 months to alleviate the subject burden of having BMA done at 3 months before first dose.
	Added to footnote i clarification on collection of MF-SAF v4.0 assessment during screening and throughout the study.	Clarification.
	Modified footnote n to clarify subjects receiving treatment other than ruxolitinib will undergo a washout period of 7 days prior to treatment with NS-018.	Clarification.
	Added footnote q and included "q" to the assessment of Concomitant therapies/procedures/medication assessment.	Clarification.
2.2 Background	Revised "30 da" to survival	Typographical error correction.
Section 1.3, Global Schedule of Assessments 4.1 Overall Design Appendix 3 Clinical Laboratory Tests Appendix 15 Schedule of Assessment for South Korea Only Appendix 16 Schedule of Assessment for UK Only Appendix 17 Schedule of Assessment for Germany Only	Added that all subjects will be evaluated for active tuberculosis and inactive (latent) tuberculosis testing will be done in UK and South Korea by local laboratory. Clarified in footnote f that total bilirubin is collected for safety assessments. Added direct bilirubin for screening.	Clarification.
5.1 Inclusion Criteria #6	Added that each platelet count result must be <50,000/µL.	Clarification.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria #7	Added subjects who are not benefitting from ruxolitinib may be enrolled per the Investigator's discretion. JAK-inhibitor was replaced with ruxolitinib as MF-directed treatment, while clarifying the washout period before starting NS-018 at Cycle 1 Day 1	Clarification.
5.1 Inclusion Criteria #16	Added specific contraception requirements and pregnancy testing for Germany and UK only for male and female subjects.	Text was revised to clarify that male subjects must refrain from donating sperm for the duration of the study and for 180 days after study completion or following discontinuation of study treatment. Text was revised to clarify that male subjects with partners who are WOCBP, pregnant or breastfeeding must agree to remain abstinent from penile vaginal intercourse throughout the study treatment period until 180 days from last study treatment.
5.2 Exclusion Criteria #1	Added that the inactive (latent) tuberculosis testing to be done for UK and South Korea only.	Clarification.
5.2 Exclusion Criteria #2	Revised prior treatment with 1 JAK inhibitors to 2 JAK inhibitors.	To enhance enrollment.
5.2 Exclusion Criteria #3a and 3b	Deleted the duration of treatment is cumulative and excludes dose interruptions and loss of spleen response.	To enhance enrollment.
5.2 Exclusion Criteria #3	Added subject receiving clinical benefit from JAK inhibitor is allowed per the investigator's discretion.	To enhance enrollment.

Section # and Name	Description of Change	Brief Rationale
5.4 Screen Failures	Added that rescreened subjects should be given a new screening number and will require re-consenting.	Clarification.
6.1 Study Treatment(s) Administered	Added subjects transitioning from BAT to NS-018 will receive study drug (NS-018) at Day 1 of every 3 cycles.	Clarification.
6.6 Dose Modification	Added thrombocytopenia with active bleeding to Grade 4 for drug-related AEs and management of hematologic AEs. Added Grade 3 or Grade 4 non-hematologic AEs will require dose interruption or dose reduction for non-hematologic AEs.	Clarification.
8.1.3 Bone Marrow Assessment	Modified bone marrow assessment from 3 months to 6 months. Deleted the timepoint for bone marrow assessment at Cycle 7 Day 1.	Baseline bone marrow assessment was changed from 3 to 6 months to alleviate the subject burden of having BMA done at 3 months before first dose.
8.1.4 Myelofibrosis Symptom Assessment Form Appendix 15 Schedule of Assessments for South Korea Only	Added clarification on when MF-SAF v4.0 assessment will be collected during screening and throughout the treatment period. Removed the following text: Usability testing on selected electronic platforms should be completed in order to ensure that subjects can use the electronic devices appropriately.	Clarification and was removed to reduce the complexity. The text was removed because usability testing is not a protocol requirement. Usability testing of the platforms was done during user acceptance testing of the device and platforms.

Section # and Name	Description of Change	Brief Rationale
	Removed the following text: Subjects transitioning from BAT to NS-018 treatment at any time before Cycle 7 Day 1 will complete the MFSAF v4.0 daily assessments for the first 7 days prior to start of NS-018 treatment. Additionally, MFSAF v4.0 assessments will be completed daily for 7 days after each cycle until the end of Cycle 12 (Day 336).	The text was removed to reduce the complexity.
8.1.5.2.1 Phospho-STAT3 Assessments	Revised collection of phospho-STAT3 for Cycle 2 Day 1 from 24 hours to 1 hour after administration of NS-018.	Clarification.
	Added NS -018 arm only for participation in phospho-STAT3 is optional and based on the site's capability to process the sample prior to shipment to the central laboratory.	Clarification.
8.1.6.1 Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form (F-SF) 7b	Removed the following text: Subjects transitioning from the BAT to NS-018 treatment at any time before Cycle 7 Day 1 will complete PROMIS F-SF daily assessments for the first 7 days prior to start of NS-018 treatment. Additionally, this assessment will be completed daily for the last 7 days after each cycle until the end of Cycle 12 (Day 336).	The text was removed to reduce the complexity.

Section # and Name	Description of Change	Brief Rationale
8.2.1 Physical Examinations	Added for subjects in UK only, a skin examination will also be conducted as part of the physical examination. Modified spleen measurement from 10 days to 14 days	This was added as the ruxolitinib SmPC indicates that periodic skin examination is recommended for subjects. The collection of skin cancer data as an AESI was considered insufficient to meet this requirement and to provide additional time for sites to upload the MRI scan for eligibility assessment for spleen measurement.
8.2.3 Electrocardiograms	Revised ECG is required at screening for all subjects and will be collected after randomization at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 4 Day 1, and Day 1 of every 3 cycles thereafter.	Clarification.
	Clarified that subjects transitioning from BAT to NS-018 will have ECG done on Day 1 and Day 15 of the first cycle of NS-018, Day 1 of the second and fourth cycles, and Day 1 of every three cycles thereafter.	Clarification.
	Added for UK only and South Korea only, collection and timing of ECGs during Cycles.	The additional ECG was in response to the competent authority's request.
Appendix 2 Regulatory, Ethical, and Study Oversight Considerations	Added pSTAT3 assessment as a function and Cerba is the responsible organization.	Clarification.
	Added mRNA assessment and Takara-Bio as responsible organization	Clarification.

Section # and Name	Description of Change	Brief Rationale
Appendix 3 Clinical Laboratory Tests	Additional laboratory testing may be performed per the local standard of care. Clarified that latent TB test at Screening to be performed only for Korea and UK Clarified that local lab assessments will be performed per investigator's discretion to monitor safety. Included "active TB test" at screening (except for the UK).	Clarification.
Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information	Added intrauterine hormone-releasing system (Italy only) for highly effective contraceptive methods.	Clarification.
	Added Investigators are to collect data on all female subjects who become pregnant, definition of AE or SAE on pregnancy, and that any subject who becomes pregnant during the study will discontinue study treatment or be withdrawn from the study.	Clarification.
	Added additional contraceptive guidance for male subjects.	Clarification.
Appendix 7 Contraceptive Guidance and Collection of Pregnancy Information for Germany and United Kingdom	Added entire Appendix 7 for contraceptive guidance and collection of pregnancy information for Germany and United Kingdom.	To reflect the changes requested by the UK Medicines & Healthcare products Regulatory Agency
Appendix 9 Primary Myelofibrosis Definition	Added Serum to LDH level.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Appendix 15 Schedule of Assessments for South Korea Only	Modified the Visit Windows from plus/minus to only plus 3 days.	To facilitate the collection of PROMIS diary data for the last 7 days of each cycle.
	Added footnote g to 12-lead ECG assessments in the table where appropriate.	Clarification.
	Added to footnote i clarification on collection of MF-SAF v4.0 assessment during screening and throughout the study.	Clarification.
	Added to footnote b 14 days for spleen measurement.	To provide additional time for sites to upload the MRI scan for eligibility assessment.
	Modified footnote f to clarify safety laboratory assessments and timing.	Clarification.
	Modified footnote g to clarify ECGs timing.	Clarification.

Section # and Name	Description of Change	Brief Rationale
	Modified footnote h bone marrow assessment was modified from 3 months to 6 months. Modified footnote n to clarify subjects receiving treatment other than JAK inhibitor will undergo a washout period of 7 days prior to treatment with NS-018.	Clarification.
	Additional assessment guidance was also added to South Korea SOA.	Clarification.
Appendix 16 Schedule of Assessments for UK only	Added schedule of assessment specific to UK and additional guidance for UK only.	Provided study assessment schedule to address UK site only.
Appendix 17 Schedule of Assessments for Germany only	Added schedule of assessment specific to Germany.	Provided study assessment schedule to address Germany site only.
Appendix 18 Protocol Amendment History	Added protocol amendment summary of changes table from original protocol Version 1.0 to Version 2.0.	Added document history of protocol amendment.

The following country-specific protocols were consolidated in this amendment.

Document	Date	Date of Approval by Competent Authority
Italy Protocol V1.1	28 October 2022	07 February 2023
United Kingdom Protocol V1.2	19 July 2022	02 November 2022
Germany Protocol V1.2	25 August 2022	16 January 2023

Changes that are country-specific for Germany, Italy, and UK are identified, respectively, in the following sections.

Germany Protocol V1.2

Germany protocol version 1.2, dated 25 August 2022, was amended based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union in a letter dated 19 May 2022, because it significantly impacts the safety or physical/mental integrity of subjects or the scientific value of the study, given the phase of this study, study population and expected menopausal status/use of contraception for the enrolled subjects.

Overall Rationale for the Germany Amendment:

The following table is the summary of changes requested and approved by the Germany Federal Institute for Drugs and Medical Devices in a letter dated 16 January 2023 and consolidated in this global amendment.

Section # and Name	Description of Change	Brief Rationale
Section 8.2, Safety Assessments Appendix 17 Schedule of Assessment for Germany Only	Added text under "Safety Assessments" to specify to closely monitor safety of BAT patients transitioning to NS-018.	Text was updated, as NS-018 has very limited clinical data to date, and an adjustment of the test plan to closely monitor safety of BAT subjects transitioning to NS-018 was required. This change was not included in amendment version 1.1 as initially requested by the Germany Federal Institute for Drugs and Medical Devices in a letter dated 10 Feb 2022 and is now included in this amendment version 1.2.
Section 5.1, Inclusion Criteria 16	Revised text.	Text was revised to delete any specific information and to refer to protocol Appendix 7, to avoid conflicting information defined in Appendix 6 and to clarify the contraception requirements. Text referring to complete abstinence, double-barrier method, tubal ligation or vasectomy were removed.
Section 11.0, Appendix 6 (Contraceptive Guidance and Collection of Pregnancy Information)	Revised text under "Male subjects" to clarify sperm donation and the use of condom.	Text was revised to clarify that male subjects must refrain from donating sperm for the duration of the study and for 180 days after study completion or the last dose of study treatment. Text was revised to clarify that male subjects with partners who are WOCBP, pregnant or breastfeeding must agree to remain abstinent from penile vaginal intercourse throughout the study treatment period until 180 days from last study treatment. The use of condom was also removed from the text given that it is not "highly effective" as per the CTFG contraception guidance – subsection 4.2.

Section # and Name	Description of Change	Brief Rationale
	Revised text under "Female subjects" to clarify contraceptive use.	Text was revised for female subjects that they must use 2 highly effective contraceptive methods during the study and for 180 days after last dose of NS-018 as per Appendix 6 guidance for males, or for the duration required by product information of the comparator drug.
	Added text under "Female subjects" to follow the contraception requirements of comparator therapies.	Added text to state that contraception requirements of comparator therapies must be followed. As these comparator therapies are started in this protocol, this advice must be included in the protocol.
	Removed footnote b from table for "Highly Effective Contraceptive Methods" and replaced with revised text. Removed "hormonal contraception methods" clarifying that they cannot be used.	Text was revised to state that hormonal contraception methods are not allowed to be used. The IB indicates that NS-018 may be susceptible to drug-drug interactions and no results of clinical drug-drug interaction studies are provided. Therefore, hormonal contraception will not be allowed, and this option was removed from the protocol.
	Added the following text under "Pregnancy Testing": "Monthly pregnancy tests should be performed for WOCBP. The serum pregnancy test should not be older than 72 hours before taking the first dose of study treatment.".	Text was revised based on incomplete preclinical toxicity testing program and related toxicity as described in the IB.
Throughout	Text edits.	Minor editorial changes were made for consistency.

Italy Protocol Version 1.1

Overall Rationale for the Italy Amendment:

Italy protocol version 1.1, dated 28 October 2022, was amended to incorporate the changes requested from the Italian Medicines Agency, Agenzia Italiana del Farmaco (AIFA) in a letter dated 26 July 2022.

The following table is the summary of changes requested and approved by the Italian Medicines Agency, Agenzia Italiana del Farmaco (AIFA) in a letter dated 07 February 2023 and consolidated in this global amendment.

Section # and Name	Description of Change	Brief Rationale
Throughout	Updated with edits, such as replacing abbreviations with spelled out words and corrections of misspelled words, that were made in various sections throughout the protocol.	For added clarity and per standard style guide.
Section 1.1 Synopsis Section 4.1 Overall Design	The following sentences were removed. Subjects treated with a JAK inhibitor will be required to taper of this treatment before initiation of NS 018 at Cycle 1 Day 1. The dose of JAK inhibitor should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration for the total tapering period of 14 days. JAK inhibitor should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of a JAK inhibitor are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of a JAK inhibitor therapy) is noted, it is strongly suggested that therapy with a JAK inhibitor be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended.	To be consistent with inclusion criteria #7 that was changed as requested by the Italian Medicines Agency.
Section 2.2 Background	Replaced “30 da” with “survival” after “shortened”	Typographical error correction.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	The following inclusion criteria #7 was removed as it is only applicable for Italy. "Subjects treated with a JAK inhibitor will be required to taper of the JAK inhibitor before initiation of NS-018 at Cycle 1 Day 1. The dose of JAK inhibitor should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration for the total tapering period of 14 days. JAK inhibitor should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of a JAK inhibitor are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of a JAK inhibitor therapy) is noted, it is strongly suggested that therapy with a JAK inhibitor be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended." The following sentence was added. "Subjects who are not benefitting from ruxolitinib treatment may be enrolled in the study per the Investigator's discretion."	Inclusion criteria #7 was changed as requested by the Italian Medicines Agency.
Section 5.2 Exclusion Criteria	The following criteria was added. 3. Subjects receiving any clinical benefits from JAK inhibitor per the Investigator's discretion.	Exclusion criteria 3. was added to reinforce the change in inclusion criteria #7 as requested by the Italian Medicines Agency.

United Kingdom Protocol Version 1.2

Overall Rationale for the United Kingdom Amendment:

United Kingdom (UK) protocol version 1.2, dated 19 July 2022, was amended to incorporate the changes requested by the UK Medicines and Healthcare products Regulatory Agency (MHRA) in a letter dated 26 May 2022.

The following table is a summary of changes requested and approved by the MHRA in a letter dated 02 November 2022 and consolidated in this global amendment.

Section # and Name	Description of Change	Brief Rationale
Section 5.1, Inclusion Criteria 16	Revised text.	Text was revised to delete any specific information and to refer to protocol Appendix 7, to avoid conflicting information defined in Appendix 6 and to clarify the contraception requirements. Text referring to complete abstinence, double-barrier method, tubal ligation or vasectomy were removed.
Section 11.0, Appendix 6 (Contraceptive Guidance and Collection of Pregnancy Information)	Revised text under "Male subjects" to clarify sperm donation and the use of condom.	Text was revised to clarify that male subjects must refrain from donating sperm for the duration of the study and for 180 days after study completion or the last dose of study treatment. Text was revised to clarify that male subjects with partners who are WOCBP, pregnant or breastfeeding must agree to remain abstinent from penile vaginal intercourse throughout the study treatment period until 180 days from last study treatment. The use of condom was also removed from the text given that it is not "highly effective" as per the Clinical Trial Facilitation Group contraception guidance – subsection 4.2.
	Revised text under "Female subjects" to clarify contraceptive use.	Text was revised for female subjects that they must use 2 highly effective contraceptive methods during the study and for 180 days after last dose of ilginatinib as per Appendix 6 guidance for males, or for the duration required by product information of the comparator drug.
	Added text under "Female subjects" to follow the contraception requirements of comparator therapies.	Added text to state that contraception requirements of comparator therapies must be followed. As these comparator therapies are started in this protocol, this advice must be included in the protocol.

Section # and Name	Description of Change	Brief Rationale
	Removed footnote b from table for "Highly Effective Contraceptive Methods" and replaced with revised text. Removed "hormonal contraception methods" clarifying that they cannot be used.	The text in footnote b was unclear and also made the unclarified recommendation to use 2 highly effective methods, which could mean 2 types of hormonal methods, or 1 type of hormonal method combined to another highly effective method. Text was revised to state that hormonal contraception methods are not allowed to be used. The IB indicates that ilginatinib may be susceptible to drug-drug interactions and no results of clinical drug-drug interaction studies are provided. Therefore, hormonal contraception will not be allowed, and this option was removed from the protocol.
Throughout	Text edits.	Minor editorial changes were made for consistency

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2b, Open-label, Multicenter, Randomized, Controlled, 2-Arm Study to Assess the Efficacy and Safety of Orally Administered NS-018 versus Best Available Therapy in Subjects with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis with Severe Thrombocytopenia (Platelet Count <50,000/μL)

Study Rationale:

NS-018 is a potent and specific Janus kinase 2 (JAK2) inhibitor which was designed and synthesized by Nippon Shinyaku Co., Ltd. NS-018 is being developed as a therapeutic agent for myeloproliferative neoplasm (MPN) including myelofibrosis (MF). A Phase 1/Phase 2, multicenter, dose-escalation, open-label study of NS-018 was conducted in subjects with primary myelofibrosis (PMF), post-polycythemia vera MF (PVMF), or post-essential thrombocythemia MF (ETMF) with 10 dosing cohorts (Study No. NS-018-101 [NCT01423851]). A total of 48 evaluable subjects were enrolled in the Phase 1 part of the study. The best response in palpable spleen size reduction of ≥50% observed was similar between subjects administered with 300 mg once daily (QD) and twice daily (BID), which is 56% (5/9) and 50% (3/6), respectively. In terms of safety, both 300 mg QD and 300 mg BID were tolerable. The safety data showed a difference between 300 mg QD (17%, 1/6) and 300 mg BID (50%, 4/8) in dose reduction or discontinuation up to Cycle 7 Day 1 (first dose cohort). The 300 mg QD dose was selected as the dose for the Phase 2 part of Study NS-018-101. A total of 29 evaluable subjects were enrolled in the Phase 2 part of Study NS-018-101. In the Phase 2 part of the study, spleen volume reduction (SVR) was measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan. There were no safety concerns in subjects administered with 300 mg QD; however, only 1 subject with a baseline platelet count of <50,000/μL achieved ≥35% reduction in spleen size volume as measured by MRI at Cycle 7. There was a trend, however, that subjects with higher area under the plasma concentration-time curve (AUC) obtained higher efficacy in terms of SVR and an improvement of symptoms. In the Phase 1 part of Study NS-018-101, there was no clear difference in drug-related hematological adverse events (AEs) between 300 mg QD and 300 mg BID (Grade 3/4 thrombocytopenia: 13% (2/15) and 8% (1/12), Grade 3/4 anemia: 0% and 17% (2/12), respectively. The safety assessment of 300 mg QD showed no clear difference from 300 mg BID in terms of drug-related non-hematological AEs (gastrointestinal disorders 4/15 [27%] versus 6/12 [50%]; nervous system disorders 6/15 [40%] versus 5/12 [42%]), with dizziness and nausea the most common toxicities in these classes, respectively.

In reviewing the available data, the following 3 factors were considered in the selection of subjects with severe thrombocytopenia (platelet count <50,000/μL) and the 300 mg BID dose that will be used in the NS-018-201 study: 1) 300 mg BID safety profile that was demonstrated in the Phase 1 part of Study NS-018-101 (n=12); 2) demonstrated efficacy of >35% SVR as measured by MRI at Cycle 7 in 1 subject with baseline platelet count of <50,000/μL who received 300 mg QD in the Phase 2 part of Study NS-018-101; and 3) detected trend in higher efficacy in SVR and improvement in symptoms in those subjects with higher AUC.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of the dose of 300 mg BID of NS-018 to the BAT, in subjects with PMF, post-PVMF, or post-ETMF with severe thrombocytopenia. • To compare the effect on MF-associated symptoms as measured by (MF-SAF v4.0 to the BAT.	• Proportion of subjects who achieve ≥35% reduction in spleen volume from baseline to Week 24 as measured by MRI (or by CT for applicable subjects). • Proportion of subjects who achieve ≥50% reduction in total symptom score from baseline to Week 24 as measured by the MF-SAF v4.0.
Secondary	
• To compare the best splenic response of 300 mg BID of NS-018 to the BAT. • To compare the safety of 300 mg BID of NS-018 to the BAT.	• Proportion of subjects who achieve ≥35% reduction in spleen volume from baseline at any time up to Week 24 as measured by MRI (or by CT for applicable subjects). • Comparison of the safety of NS-018 versus BAT.

Abbreviations: BAT=Best Available Therapy; BID=twice daily; CT=computed tomography; ETMF=essential thrombocythemia myelofibrosis; F-SF = Fatigue Short Form; mRNA=messenger ribonucleic acid; IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; MF=myelofibrosis; MF-SAF v4.0=Myelofibrosis Symptom Assessment Form version 4.0; MRI=magnetic resonance imaging; PMF = primary myelofibrosis; PVMF = polycythemia vera myelofibrosis.

Study Population:

The population for this study includes male and female subjects who are 18 years of age or older with PMF, post-PVMF, or post-ETMF with severe thrombocytopenia (platelet count <50,000/μL), including subjects with intermediate-2 or high-risk MF according to the Dynamic International Prognostic Scoring System (DIPSS), and who require therapy. Subjects must have spleen volume of at least 450 cm^3 measured by MRI (or by CT for applicable subjects) and have an Eastern Cooperative Oncology Group performance status of ≤2 at study entry (screening). Subjects may or may not have received prior therapy for MF including JAK inhibitor.

Overall Study Design:

This is a Phase 2b, open-label, multicenter, randomized, controlled, 2-arm study in subjects with PMF, post-PVMF, or post-ETMF to compare the efficacy and safety of NS-018 versus BAT. Subjects will be stratified at baseline by spleen volume and by history of prior JAK inhibitor treatment and randomized to receive either NS-018 or BAT (control group). The stratification factors will be as follows: 1) spleen volume [redacted]; 2) JAK inhibitor (naïve versus prior treatment). There will be no MF-directed treatment (other than JAK inhibitor) for at least 2 weeks prior to initiation of NS-018 or BAT.

NS-018 Dosage and Mode of Administration

NS-018 will be self-administered orally at a dose of 300 mg BID. The BAT will be administered according to product label and Investigator's discretion.

Best Available Therapy Dosage

The Investigator will decide the BAT that will be administered to the subject during the screening period based on subject's condition. The BAT must be one of the following: hydroxyurea, danazol, fedratinib, ruxolitinib, interferon, corticoid, erythropoietin, purinethol, thalidomide, lenalidomide or 'supportive

care/therapy'. The BAT should be administered according to the manufacturer's instructions or the Investigator's discretion. The BAT is 'supportive care/therapy', and refers to use of blood products, fluids (crystalloids), pain medications, and/or antibiotics, that subjects will need to manage myelofibrosis symptoms and complications. Subjects in the control group will receive BAT at doses and schedules selected by the Investigator based on the subject's condition and according to the manufacturer's instructions or the Investigator's discretion. The BAT must be a single agent and cannot be combined with other agents. JAK inhibitor can be allowed as BAT if the JAK inhibitor was administered as a standard of care based on the product label or Investigator's discretion. The BAT may be changed at any time during the randomized treatment period based on the Investigator's clinical assessment of the subject's condition. However, it is not allowed to change the BAT to JAK inhibitor if it was not used as standard of care treatment prior to study participation. . No experimental agents (ie, those not approved for any indication) may be used at any time.

Study Visits

Subjects will have regular scheduled study visits at screening, Day 1, Day 15 of Cycles 1, 2, 3, 4, 5, and 6, and Day 1 of every cycle thereafter. One cycle is 28 days. Subjects transitioning from BAT to NS-018 before or at Cycle 7 Day 1 will have safety laboratory assessments performed on Day 1 and Day 15 of each cycle for 6 cycles. Safety laboratory assessments will continue on Day 1 of the following cycles until the end of the study and will be done by a central laboratory (refer to Appendix 17 SoA for further details). Additional local laboratory assessments may be performed per Investigator's discretion to monitor safety and document AEs as per local standards of care.

Subjects in South Korea only, safety laboratory assessments will be performed weekly at Cycle 1 on Day 1, Day 8, Day 15, and Day 22, and Cycles 2 through 6 will be performed on Days 1 and 15, and Day 1 of each cycle thereafter. Laboratory visits on Day 8 and Day 22 of Cycle 1 for subjects randomized to NS-018 or Cycle 1 after transitioning to NS-018 in subjects who transition to NS-018 will be performed at the institutional local laboratory (refer to Appendix 15 SoA for further details).

Subjects who transition from BAT to NS-018 will have a physical examination done on Day 1 of each cycle for the first 4 cycles after transitioning to NS-018 and on Day 1 of every three cycles thereafter, as subjects are transitioned to NS-018. Vital signs will be done on Day 1 of each cycle after transitioning to NS-018. Vital signs will be taken within 3 hours before transitioning to NS-018. Electrocardiogram (ECG) will be done on Day 1 and Day 15 of the first cycle and on Day 1 of the second and fourth cycles after transitioning to NS-018, and on Day 1 of every 3 cycles thereafter as subjects randomized to NS-018. Each ECG measurement will be performed 2 hours (±10 minutes) postdose.

Subjects treated with ruxolitinib will be required to taper off this treatment before initiation of NS-018 at Cycle 1 Day 1. The dose of ruxolitinib should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration of total tapering period of 14 days. Ruxolitinib should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of ruxolitinib as standard of care prior to study participation, are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms upon discontinuation of ruxolitinib therapy is noted, it is strongly suggested that therapy with ruxolitinib be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended.

Eligible subjects will receive NS-018 or BAT according to treatment assignment from Cycles 1 to 6 until one of the following criteria for disease progression is met:

1. Increase in spleen volume of ≥15% measured by MRI (or by CT for applicable subjects) from the baseline for subjects who are randomized to NS-018 or transitioned to NS-018.
2. Splenic irradiation or splenectomy.
3. Leukemic transformation defined by an increase in peripheral blood blast percentage to ≥20% that is sustained for at least 8 weeks.
4. Leukemic transformation defined by bone marrow blast count of ≥20%.
5. Death.

Subjects who meet the criteria for increase in spleen volume of >15% measured by MRI (or by CT for applicable subjects), leukemic transformation, or have had splenic irradiation will be discontinued from the study treatment and will be asked to complete the end of study procedures. Subjects randomized to the BAT arm (ie, subjects already on BAT or 'supportive care/therapy' and met all of the following criteria may transition to NS-018 treatment.

- Subject has completed at least 24 weeks on BAT or had progression of disease prior to Week 24; progression must be declared based only on an increase in splenic volume of >15% measured by MRI (or by CT for applicable subjects) from baseline.
- Subject has not undergone splenic irradiation or splenectomy.
- Subject does not meet criteria for leukemic transformation.

There will be no MF-directed treatment (other than ruxolitinib) for at least 1 week (7 days) prior to initiation of NS-018 after completion of BAT. Changes in the MF-directed treatment should be documented.

Subjects randomized to receive either NS-018 or BAT may continue to receive NS-018 after completion of Cycle 6. In the BAT treatment arm (control group), after subjects have completed treatment with BAT at the end of Cycle 6, the Investigator will determine whether subjects should continue BAT treatment outside the study (ie, withdrawn from the study) or discontinue BAT and transition to NS-018 at Cycle 7 Day 1. During this transition period, subjects treated with ruxolitinib will be required to taper off this treatment before initiation of NS-018. The dose of ruxolitinib should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration for the total tapering period of 14 days. Ruxolitinib should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of ruxolitinib are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of ruxolitinib therapy) is noted, it is strongly suggested that therapy with ruxolitinib be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended.

Subjects receiving treatment other than ruxolitinib will undergo a minimum washout period of 1 week (7 days) prior to start of NS-018 treatment.

For subjects receiving BAT and transitioning to NS-018 before Cycle 7 Day 1, subjects will be required to taper off or washout this treatment before initiation of NS-018 as described above.

Subjects may continue to receive treatment with NS-018 until the subject meets the discontinuation criteria of study treatment (see Section 7.1 of protocol), or until 3 years (expected) after the first subject is enrolled at any of the study centers, whichever comes first. Dose modification is allowed for subjects who experience Grade 4 neutropenia, lymphopenia or bleeding, or Grade 3 or 4 non-hematologic AEs (see Section 6.6 of protocol).
Visits for subjects in South Korea, UK, and Germany are detailed in a separate schedule of assessments (SoA) in Appendix 15, Appendix 16, and Appendix 17, respectively.

Number of Investigators and Study Centers:

A total of 65 Investigators and study centers in multiple countries are expected to participate in this study. Additional study centers may be added to support enrollment.

Number of Subjects:

A total of 120 subjects are expected to be enrolled and randomized 1:1 to either of the following treatment arms:

- NS-018
- BAT

See Section 9.2 of the protocol.

Treatment Groups and Duration:

Individual subject participation will depend upon the ability to tolerate the treatment regimen and upon the time to a progression event mandating study withdrawal.
The screening period is 28 days before start of treatment. During screening, all subjects will be evaluated for active tuberculosis. Additionally, inactive (latent) tuberculosis testing will be done in UK and South Korea by local laboratory for all subjects. At Cycle 1 Day 1, before the subject starts study treatment, all eligibility criteria including the subject's status for coronavirus disease 2019 (COVID-19) must be reviewed and confirmed. All subjects will be treated from Cycle 1 Day 1 through the end of the study. There will be an indefinite period from Cycle 7 Day 1 until the subject meets the criteria of discontinuation of study treatment (see Section 7.1 of protocol), or until 3 years (expected) after the first subject is enrolled at any of the study centers, whichever comes first. All subjects will have a follow-up visit within 30 days after study completion or early termination.

Statistical Methods:

Sample size:
A total of 120 randomized subjects (60 subjects in each treatment arm) is planned. The sample size determination is based on literature.
Assuming a splenic response rate of 20% in the NS-018 arm and 1% in the BAT arm, there is 93.5% power at the final analysis to maintain a type I error rate of 5% (ie, a 2-sided significance level using Fisher's exact test is 5%). Similarly, assuming a symptom response rate of 33% in the NS-018 arm and 8% in the BAT arm, the power of the final analysis to maintain a type I error rate of 5% is 91.0%. Assuming that there is no correlation between SVR and total symptom score (TSS) reduction, the power to reject the null hypothesis for both endpoints is 85.1%.

Analysis Populations:

The intent-to-treat (ITT) population will consist of all randomized subjects.

The modified intent-to-treat (mITT) population will consist of all randomized subjects who receive at least 1 dose of study treatment and have a baseline assessment and at least 1 postbaseline efficacy assessment. Subjects will be analyzed as randomized. This will be the primary analysis population for the evaluation of efficacy.

The safety (SAF) population will consist of all randomized subjects who receive at least 1 dose of study treatment. For BAT subjects who do not receive therapy, a Cycle 1 Day 1 visit is required to be included in the SAF. Subjects will be analyzed as treated. This will be the primary analysis population for the evaluation of exposure and safety.

A second safety (SAF2) population will consist of subjects randomized to BAT who complete BAT through 6 cycles and go on to receive at least 1 dose of NS-018. Baseline will consist of the last data available prior to initiation of NS-018.

The PK concentration population will consist of all randomized subjects who receive at least 1 dose of study treatment and have at least 1 plasma concentration value for study treatment.

General Statistical Considerations:

All statistical tests will be performed at a significance level of 0.05 with no corrections for multiple comparisons.

The first primary endpoint of a proportion of subjects who achieve ≥35% SVR from baseline to Week 24 will be compared between the NS-018 group and the BAT group using Firth-corrected logistic regression model. Covariates of baseline spleen volume and a history of prior JAK inhibitor treatment will be included. Model-based point estimates for the treatment effects, 95% confidence intervals, and p-values will be calculated. Subjects who do not reach Week 24 will be considered treatment nonresponders (ie, did not achieve ≥35% SVR from baseline to Week 24). No imputations will be made for missing data.

Similar to the analysis of the first primary endpoint, the second primary endpoint of proportion of subjects who achieve ≥50% reduction in TSS from baseline to Week 24 as measured by MF-SAF v4.0 and the secondary endpoint of proportion of subjects who achieve ≥35% SVR any time up to Week 24 will be compared between the NS-018 group and the BAT group using Firth-corrected logistic regression model. Covariates of baseline spleen volume and a history of prior JAK inhibitor treatment will be included.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. For each study treatment, numbers of treatment-emergent AEs (TEAEs) and incidence rates will be tabulated by preferred term and system organ class.

Treatment-emergent AEs by maximum severity, TEAEs by relationship to study treatment, serious adverse events (SAEs), TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated for each treatment group.

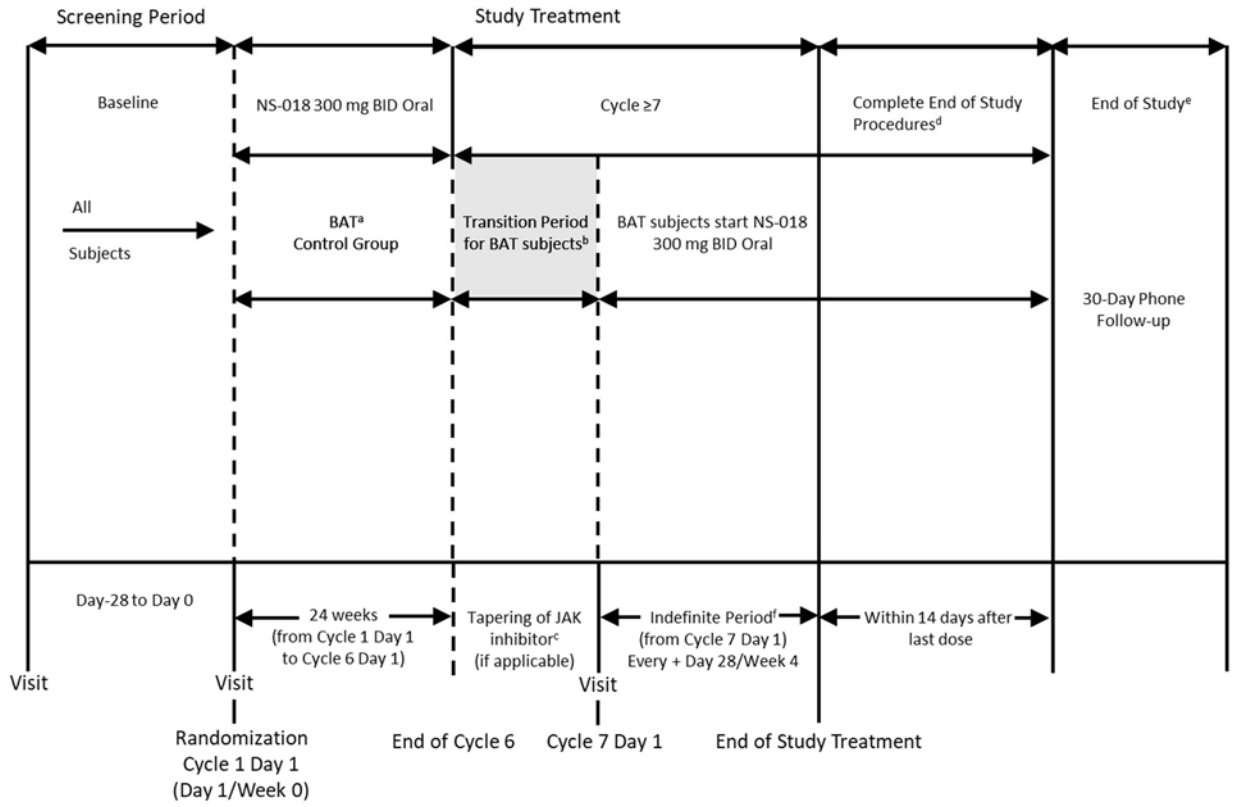
All central and local laboratory test results, vital signs measurements, electrocardiogram results, physical examination, spleen size (by palpation), spleen volume (by MRI) and weight will be summarized for each treatment group using descriptive statistics at each visit for raw numbers and change from baseline.

No interim analysis is planned for efficacy. The primary efficacy analyses will be conducted after all subjects have completed assessments at Week 24 (Cycle 7 Day 1). A final analysis will be conducted at the end of the study. An additional analysis for futility may also be performed. The statistical analysis plan will describe these analyses in greater detail.

Independent Data Monitoring Committee (IDMC):
An IDMC will be set up to oversee safety across the life span of the study and all specifics will be captured in the IDMC charter.

1.2 Schema

Figure 1 Study Schema



Abbreviations: BAT=Best Available Therapy; BID=twice daily.; JAK=Janus kinase; MF=myelofibrosis.

[a] Subjects in the control group may receive BAT at doses and schedules selected by the Investigator discretion and based on subject's condition.

[b] In the BAT treatment arm (control group), after subjects have completed treatment with BAT including BAT 'supportive care/therapy', at the end of Cycle 6, the Investigator will determine whether subjects should continue BAT treatment outside the study or discontinue BAT and transition to NS-018 at Cycle 7 Day 1. During this transition period, subjects must not receive any MF-directed treatment (other than ruxolitinib) for a minimum period of 1 week (7 days) prior to start of NS-018 treatment.

[c] Subjects treated with ruxolitinib will be required to taper off ruxolitinib before initiation of NS-018. The dose of ruxolitinib should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration for the total tapering period of 14 days. Ruxolitinib should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg once daily (QD) of ruxolitnib, are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of ruxolitinib therapy) is noted, it is strongly suggested that therapy with ruxolitinib be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended.

[d] Within 14 days after last dose of study treatment or within 14 days after withdrawal from the study.

[e] The planned end of study is the scheduled date when the final subject enrolled completes the 30-day follow-up phone call after completion of the end of study procedures.

[f] Indefinite period from Cycle 7 Day 1 until the subject experiences unacceptable toxicity that precludes any further treatment, disease progression, and/or loss of benefit from treatment, at the discretion of the Investigator, or until 3 years after the first subject in, whichever comes first.

Overview of procedures for BAT subjects transitioning to NS-018 is provided below. Sites in South Korea are to follow the SoA provided in Appendix 15. Sites in UK are to follow the SoA provided in Appendix 16. Sites in Germany are to follow the SoA provided in Appendix 17.

Additional Assessment Guidance

The table below clarifies the timing of specific assessment completion.

	BAT to NS-018 Before Cycle 7 Day 1	**BAT to NS-018 at Cycle 7 Day 1**
ECG Section 8.2.3	Day 1 and Day 15 of the first cycle, Day 1 of the second and fourth cycles, and on Day 1 of every three cycles thereafter Additionally for UK only, Day 1 on the third cycle predose (within 1 hour) and 1, 2, and 4 (±10 minutes) hours after administration of NS-018	Cycle 7 Day 1, Cycle 7 Day 15, Cycle 8 Day 1, Cycle 10 Day 1 and thereafter every 3 cycles For UK only, Cycle 9, Day 1 predose (within 1 hour) and 1, 2, and 4 (±10 minutes) hours after administration of NS-018
PK Section 8.1.5.1	No sample collection required	No sample collection required
MRI Section 8.1.2	Cycle 4 Day 1 (only if subject transitions BEFORE Cycle 4 Day 1, if subject transitions AT or AFTER Cycle 4 Day 1 then MRI is not required until Cycle 7 Day 1)	Cycle 7 Day 1, Cycle 10 Day 1, and Cycle 13 Day 1.
Safety Laboratory Assessments Section 8.2.4	Day 1 and Day 15 at Cycles 1, 2, 3, 4, 5, and 6 of NS-018 and Day 1 of each cycle thereafter until the end of the study	Day 1 and Day 15 at Cycle 7, 8, 9, 10, 11, 12 and Day 1 of each cycle thereafter until end of the study
	• Subjects in South Korea only, safety laboratory assessments will be performed weekly at Cycle 1 on Day 1, Day 8, Day 15, and Day 22, and Cycles 2 through 6 will be performed on Days 1 and 15, and Day 1 of each cycle thereafter. Laboratory visits on Day 8 and Day 22 can be done at a local laboratory. .	

Abbreviations: BAT = best available therapy; C = cycle; C7D1 = Cycle 7 Day 1; D = Day;
ECG = electrocardiogram; MRI= magnetic resonance imaging; PK = pharmacokinetics; UK = United Kingdom.

1.3 Global Schedule of Assessments

All sites unless otherwise specified are to follow the Global SoA (Section 1.3). Sites in South Korea are to follow the SoA provided in Appendix 15. Sites in United Kingdom (UK) are to follow the SoA provided in Appendix 16. Sites in Germany are to follow the SoA provided in Appendix 17.

Visit Timing	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**	
	Day −28 to Day 0	**Day 1 (Day 1/ WK 0)**	**Day 15 (Day 15/ WK 2)**	**Day 1 (Day 29/ WK 4)**	**Day 15 (Day 43/ WK 6)**	**Day 1 (Day 57/ WK 8)**	**Day 15 (Day 71/ WK 10)**	**Day 1 (Day 85/ WK 12)**	**Day 15 (Day 99/ WK 14)**
Visit Window			**+ 3 days**	**+ 3 days**	**+ 3 days**	**+ 3 days**	**+ 3 days**	**+ 3 days**	**+ 3 days**
Study Procedure									
Informed consent	X								
Review/confirm eligibility criteria	X	X							
COVID-19 status verification	X								
Genetic substudy informed consent (optional)	X								
Medical history	X[a]								
Physical examination	X[b]			X[c]		X[c]		X[c]	
MRI/CT (spleen volume measurement)	X[d]							X	
Vital signs	X	X		X		X		X	
ECOG PS	X	X[e]							
Active tuberculosis	X								
Clinical laboratory[f] (by central lab)	X	X[e]	X	X	X	X	X	X	X
Pregnancy test (serum)	X								
12-lead ECG	X[g]	X[g]	X[g]	X[g]				X[g]	

Visit Timing	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	Day −28 to Day 0	Day 1 (Day 1/ WK 0)	Day 15 (Day 15/ WK 2)	Day 1 (Day 29/ WK 4)	Day 15 (Day 43/ WK 6)	Day 1 (Day 57/ WK 8)	Day 15 (Day 71/ WK 10)	Day 1 (Day 85/ WK 12)	Day 15 (Day 99/ WK 14)
Visit Window			+ 3 days	+ 3 days	+ 3 days	+ 3 days	+ 3 days	+ 3 days	+ 3 days
PK sampling (NS-018 treatment arm only)		X		X					
Bone marrow assessment	X[h]								
Response assessment (IWG-MRT and ELN)				X		X		X	
Genetic profiling		X[e]							
Phospho-STAT3 (NS-018 treatment arm only)		X[e]		X					
mRNA sequencing (NS-018 treatment arm only)		X[e]		X					
MF-SAF v4.0[i]	←								→
PROMIS[j]	←								→
EQ-5D-5L		X[e]							
Randomization		X[m]							
Dispense study treatment/diary		X[e]		X		X		X	
Administer study treatment (NS-018)		←							→
Administer study treatment (BAT)[n]		←							→
AEs	X	X[e]	X	X	X	X	X	X	X
Concomitant therapies/procedures/medication	X	X[e]	X	X	X	X	X	X	X

Visit Timing	**Cycle 5**		**Cycle 6**		**Cycle ≥7**	**Complete End-of-Study Procedures[l, o]**	**End of Study**
	Day 1 (Day 113/ WK16)	**Day 15 (Day 127/ WK18)**	**Day 1 (Day 141/ WK20)**	**Day 15 (Day 155/ WK22)**	**Day 1 (Every +Day28/WK4)**		**30-Day Follow-up (Phone call)[p]**
Visit Window	**+ 3 days**	**+ 3 days**	**+ 3 days**	**+ 3 days**	**± 1 week**		**± 3 days**
Study procedure							
Informed consent							
Review/confirm eligibility criteria							
Medical history							
Physical examination					X[c] (Every 3 cycles)	X[b]	
MRI/CT (spleen volume measurement)					X (Cycles 7, 10, 13)	X[k]	
Vital signs	X		X		X	X	
ECOG PS						X	
Clinical laboratory[f] (by central lab)	X	X	X	X	X	X	
Pregnancy test (serum)						X	
12-lead ECG (NS-018 treatment arm only at/after C1D1)[g]					X (Every 3 cycles)	X	
PK sampling (NS-018 treatment arm only)							
Bone marrow assessment					X (Cycles 13; every 12 cycles thereafter)		

Visit Timing	**Cycle 5**		**Cycle 6**		**Cycle ≥7**	**Complete End-of-Study Procedures[l, o]**	**End of Study**
	Day 1 (Day 113/ WK16)	**Day 15 (Day 127/ WK18)**	**Day 1 (Day 141/ WK20)**	**Day 15 (Day 155/ WK22)**	**Day 1 (Every +Day28/WK4)**		**30-Day Follow-up (Phone call)[p]**
Visit Window	**+ 3 days**	**+ 3 days**	**+ 3 days**	**+ 3 days**	**± 1 week**		**± 3 days**
Response assessment (IWG-MRT and ELN)					X (Every 3 cycles)	X	
Genetic profiling							
Phospho-STAT3 (NS-018 treatment arm only)							
mRNA sequencing (NS-018 treatment arm only)							
MF-SAF v4.0[i]	→	→	→	→	→ (Up to Cycle 12)		
PROMIS[j]	→	→	→	→	→ (Up to Cycle 12)		
EQ-5D-5L					X (Every 6 cycles)		
Randomization[m]							
Dispense study treatment/diary	X		X		X (Every 3 cycles)		
Administer study treatment (NS-018)	→	→	→	→	→		
Administer study treatment (BAT)[n]	→	→	→	→	(Transition to NS-018)		

Visit Timing	Cycle 5		Cycle 6		Cycle ≥7	Complete End-of-Study Procedures[l, o]	End of Study
	Day 1 (Day 113/ WK16)	Day 15 (Day 127/ WK18)	Day 1 (Day 141/ WK20)	Day 15 (Day 155/ WK22)	Day 1 (Every +Day28/WK4)		30-Day Follow-up (Phone call)[p]
Visit Window	**+ 3 days**	**+ 3 days**	**+ 3 days**	**+ 3 days**	**± 1 week**		**± 3 days**
AE	X	X	X	X	X	X	X
Concomitant therapies/procedures/ medication[q]	X	X	X	X	X	X	X

Abbreviations: AEs=adverse events; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BAT=Best Available Therapy; BUN=blood urea nitrogen; COVID-19=coronavirus disease 2019; eCRF=electronic case report form; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; ELN=European LeukemiaNet; IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; JAK=Janus kinase; LDH=lactate dehydrogenase; mRNA=messenger ribonucleic acid; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; MF=myelofibrosis; MF-SAF v4.0=Myelofibrosis Symptom Assessment Form version 4.0; MRI=magnetic resonance imaging; mRNA=messenger ribonucleic acid; PK=pharmacokinetics; STAT3=signal transducer and activator of transcription 3; PROMIS=Patient-Reported Outcomes Measurement Information System; QD=once daily; STAT3=signal transducer and activator of transcription 3; WK=week; WOCBP=women of childbearing potential.

NOTE: At Cycle 1 Day 1, before the subject starts study treatment, all eligibility criteria including the subject's COVID-19 status should be reviewed and confirmed.

NOTE: Verification of COVID-19 status is based on the World Health Organization diagnostic criteria (Public health surveillance for COVID-19. Interim guidance, 07 August 2020). If a subject presents with clinical signs and symptoms consistent with COVID-19 infection, the Investigator should request a test where possible and this should be recorded in the AE field of the eCRF.

[a] Including concomitant medications within 28 days prior to study treatment administration, blood products transfused within 3 months prior to study treatment administration, and concurrent baseline conditions.

[b] Full physical examination including weight and spleen size by clinical assessment (palpation). At screening, spleen size (palpation) measurement should be done on the same day the spleen volume is measured. If the same day measurement is not feasible, the measurement should be assessed within 14 days prior to the first dose of the study treatment.

[c] Directed physical examination including weight and spleen size by palpation. After transitioning to NS-018, the subjects will have physical examination on Day 1 of first 4 cycles and thereafter, Day 1 of every 3 cycles.

[d] Assess spleen volume within 14 days prior to the first dose of the study treatment.

[e] Predose; may be obtained within 24 hours prior to study treatment administration. AEs on Cycle 1 Day 1 will also be collected postdose.

[f] Subjects transitioning from BAT to NS-018 before or at Cycle 7 Day 1 will have safety laboratory assessments performed on Day 1 and 15 of each cycle for 6 cycles. Safety laboratory assessments will continue on Day 1 of the following cycles until the end of the study and will be done by a central laboratory. Hematology includes erythrocytes, MCV, MCH, neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin, and hematocrit. Serum chemistry includes BUN, LDH, creatinine, uric acid, total protein, albumin, glucose, direct bilirubin for screening, total bilirubin (for safety assessment), magnesium, ALP, AST, ALT, chloride, sodium, potassium, amylase, and lipase. Urinalysis includes pH, protein, glucose, ketone, bilirubin, blood, and nitrite. Note: Additional local laboratory assessments may be performed per Investigator's discretion to monitor safety and document AEs as per local standards of care.

[g] For eligibility determination and centrally read for all subjects; median QTcF must be ≤480 msec. For screening, Cycles 1 and 2, triplicate central reading, and then from Cycle 4 onwards, single central reading. ECG is required at screening for all subjects but only for NS-018 subjects at the remaining study visits. ECGs for Cycle 1 Day 1: Predose (3 time points within 1 hour) and 1, 2, 4, 6, 8 (±10 minutes) hours after administration of NS-018, Cycle 1 Day 15: 2 (±10 minutes) hours after administration of NS-018, Cycle 2 Day 1: Predose (within 1 hour) and 1, 2, 4 (±10 minutes) hours after administration of NS-018, and Cycle 4 Day 1 and thereafter every 3 cycles: 2 (±10 minutes) hours after administration of NS-018. Subjects transitioning from BAT to NS-018 before or at Cycle 7 Day 1 will have ECG done at Cycle 7 Day 1 and will follow the same visit schedule (Cycle 7 Day 15, Cycle 8 Day 1, Cycle 10 Day 1 and thereafter Day 1 of every 3 cycles).

[h] Within 28 days prior to the first dose of study drug. However, bone marrow assessment performed within 6 months prior to the first dose can be used as baseline.

[i] During the screening period, subject will complete the MF-SAF v4.0 assessment daily. The first 7 consecutive days of diary data will be used for eligibility assessment. Subject will complete the MF-SAF from Day −7 of Cycle 1 Day 1 to the end of Cycle 6 (Day 168) and the last 7 days in each cycle thereafter until the end of Cycle 12 (Day 336) for efficacy assessment.

[j] The PROMIS questionnaire must be completed daily during the screening period and the last 7 days of each cycle until the end of Cycle 12 (Day 336). This assessment will be performed for all subjects including subjects transitioning from BAT to NS-018.

[k] If not done within the previous 8 weeks.

[l] Within 14 days after last dose of study treatment or within 14 days after withdrawal from the study.

[m] Randomization can be done within Day −4 so that the subject can start study treatment on the morning of Day 1.

[n] In the BAT treatment arm (control group), after subjects have completed treatment with BAT at the end of Cycle 6, the Investigator will determine whether subjects should continue BAT treatment outside the study or discontinue BAT and transition to NS-018 at Cycle 7 Day 1. During this transition period, subjects treated with ruxolitinib will be required to taper off this treatment before initiation of NS-018. The dose of ruxolitinib should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration for the total tapering period of 14 days. Ruxolitinib should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of ruxolitinib are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of ruxolitinib therapy) is noted, it is strongly suggested that therapy with ruxolitinib be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended. Subjects receiving treatment other than ruxolitinib will undergo a minimum washout period of 1 week (7 days) prior to start of NS-018 treatment.

[o] Subjects who discontinue study treatment or withdraw from the study will be asked to complete the end of study procedures within 14 days after the last dose. If the end of study procedures occur at a regular scheduled visit, these procedures may be performed at that time.

[p] Follow-up phone call will be done 30 (±3) days after the completion of end of study procedures.

[q] Transfusion will be collected 12 weeks prior to Cycle 1 Day 1 and then throughout the study.

Additional Assessment Guidance

The table below clarifies the timing of specific assessment completion.

Assessments	Time restriction	
	Predose	**Postdose**
Pharmacokinetics (NS-018 treatment arm only)	Within 1 hour	**Cycle 1 Day 1** 0.5, 1, 2, 3, 4, 6, 8 hours (±10 min per time point) **Cycle 2 Day 1** 0.5, 1, 2, 3, 4, 6, 8 hours (±10 min per time point)
Vital signs	Within 3 hours	Not applicable
ECOG performance status	Within 24 hours	Not applicable
12-lead ECG (NS-018 treatment arm only)	**Cycle 1 Day 1** 3 time points within 1 hour (eg, -45, -30, -15 min) **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 5 time points: 1, 2, 4, 6, and 8 hours (±10 min per time point) **Cycle 1 Day 15** 2 (±10 min) hours **Cycle 2 Day 1** 3 time points: 1, 2, and 4 hours (±10 min per time point) **Cycle 4 Day 1 and thereafter every 3 cycles** 2 (±10 min) hours
Phospho-STAT3 (NS-018 treatment arm only)	**Cycle 1 Day 1** Within 24 hours **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 3 hours (±10 min) Cycle 2 Day 1 3 hours (±10 min)
mRNA sequencing (NS-018 treatment arm only)	**Cycle 1 Day 1** Within 24 hours **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 8 hours (±10 min)

Abbreviations: ECG=electrocardiogram; ECOG= Eastern Cooperative Oncology Group; min=minutes; mRNA=messenger ribonucleic acid sequencing; STAT3=signal transducer and activator of transcription 3.

2.0 INTRODUCTION

NS-018 (Ilginatinib) is a potent and specific Janus kinase 2 (JAK2) inhibitor which was designed and synthesized by Nippon Shinyaku Co., Ltd. NS-018 is being developed as a therapeutic agent for myeloproliferative neoplasm (MPN) including myelofibrosis (MF).

2.1 Study Rationale

A Phase 1/Phase 2, multicenter, dose-escalation, open-label study of NS-018 was conducted in subjects with primary myelofibrosis (PMF; defined in Appendix 9), post-polycythemia vera MF (PVMF; defined in Appendix 10), or post-essential thrombocythemia MF (ETMF; defined in Appendix 11) with 10 dosing cohorts (Study No. NS-018-101 [NCT01423851]). A total of 48 evaluable subjects were enrolled in the Phase 1 part of the study. Sequential cohorts of 3 to 6 subjects each were treated with escalating doses of NS-018. Subjects self-administered NS-018 orally. The starting dose of NS-018 was 75 mg daily. The 10 dosing cohorts were: 75 mg once daily (QD), 100 mg twice daily (BID), 125 mg QD, 200 mg QD, 200 mg BID, 250 mg BID, 300 mg QD, 300 mg BID, 400 mg QD, and 400 mg BID. Subjects were continuously treated with NS-018, administered daily therapy in 28-day cycles, until disease progression, whenever the product was tolerated. The 300 mg QD dose was selected for use in the Phase 2 part of the study. A total of 29 evaluable subjects were enrolled in the Phase 2 part of the study. Subjects were continuously treated with NS-018, administered daily therapy in 28-day cycles, until disease progression, whenever the product was tolerated.

Responses

In the Phase 1 part of Study NS-018-101, the best response in palpable spleen size reduction of ≥50% observed was similar between subjects administered with 300 mg QD and BID, which is 56% (5/9) and 50% (3/6), respectively.[1]

In the Phase 2 part of Study NS-018-101, spleen volume reduction (SVR) was measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan. Only 1 subject had ≥35% reduction in spleen size volume at Cycle 7 as measured by MRI and a baseline platelet count of <50,000/μL.

Safety findings

The maximum tolerated dose (MTD) was not reached during the Phase 1 part of Study NS-018-101 study; however, the Safety Review Committee (SRC) considered the 400 mg QD and BID cohorts not tolerable based on the proportion of drug-related neurological adverse events (AEs). A treatment-emergent AE (TEAE) was reported for all 48 subjects (100%) during the study and Grade 3 or 4 TEAEs were reported for 35 of 48 subjects (72.9%). The most frequently reported drug-related TEAEs were dizziness (11 of 48 subjects [22.9%]), anemia (10 of 48 subjects [20.8%]), thrombocytopenia (10 of 48 subjects [20.8%]),

nausea (9 of 48 subjects [18.8%]), and diarrhea (7 of 48 subjects [14.6%]). The majority of the drug-related TEAEs reported were Grade 3 in severity (16 of 48 subjects [33.3%]). No deaths were reported during the study. Any serious TEAEs were reported for 23 of 48 subjects (47.9%) and Grade 3 or 4 serious TEAEs were reported for 19 of 48 subjects (39.6%). Treatment-emergent AEs leading to discontinuation of study drug were reported for 14 of 48 subjects (29.2%). There were no apparent dose-related trends in the incidence of TEAE across the treatment groups. The SRC determined that 400 mg QD and BID were not tolerated based on the proportion of drug-related neurological AEs. Dose-limiting toxicities were observed in 2 subjects: Grade 3 QT prolongation in 1 subject in the 250 mg BID cohort and Grade 3 dizziness in 1 subject in the 400 mg BID cohort. The subject with Grade 3 QT prolongation recovered following NS-018 discontinuation. This was the only case of QT prolongation observed in the study. This was also attributed to the subject's prior cardiac history and the SRC concluded that it did not represent an overall issue for the study. The most common drug-related hematologic events were thrombocytopenia and anemia. Drug-related Grade 3/4 thrombocytopenia was reported for 13% (2/15) and 8% (1/12) in 300 mg QD and 300 mg BID, respectively. Drug-related Grade 3/4 anemia was reported for 0% and 17% (2/12) in 300 mg QD and 300 mg BID, respectively. The safety assessment of 300 mg QD showed no clear difference from 300 mg BID in terms of drug-related non hematological AEs (gastrointestinal disorders 4/15 [27%] versus 6/12 [50%]; nervous system disorders 6/15 [40%] versus 5/12 [42%]), with dizziness and nausea the most common toxicities in these classes, respectively.

In the Phase 2 part of Study NS-018-101, a TEAE was reported for all 29 subjects (100%) during the study. The most frequently reported drug-related TEAEs were diarrhea (34.5%), anemia (27.6%), fatigue (24.1%). The majority of the TEAEs reported were Grade 3 in severity (48.3%). Drug-related Grade 3 anemia and Grade 3 thrombocytopenia were reported for 21% and 3%, respectively. No case of Grade 4 TEAE was reported. A TEAE of Grade 5 in severity was reported for 1 of 29 subjects (3.4%).

Pharmacokinetics

The pharmacokinetics (PK) parameters of NS-018 were assessed in 43 subjects. On Day 8, maximum plasma concentration (C_{max}) was achieved 1 to 3 hours postdosing for all the dose cohorts. Based on C_{max} assessments on Day 8, systemic exposure of NS-018 was approximately dose proportional. The half-life of NS-018 was 2 to 4 hours. There was no evidence of drug accumulation as drug exposure was not substantially different between Day 8 and Day 29.

Based on the efficacy, safety, and PK data of the Phase 1/Phase 2 study (Study No. NS-018-101), the 300 mg BID dose of NS-018 will be examined in this Phase 2b, open-label, multicenter, randomized, controlled, 2-arm study (Study No. NS-018-201).

2.2 Background

Myelofibrosis is a BCR-ABL1-negative MPN characterized by bone marrow fibrosis, anemia, progressive splenomegaly, extramedullary hematopoiesis (EMH), debilitating constitutional symptoms, cachexia, leukemic progression, shortened survival, and compromised quality of life (QoL).[2, 3, 4] Myelofibrosis may be de novo (PMF) or secondary to polycythemia vera or essential thrombocythemia. Approximately 90% of patients with MF carry mutations in any of the 3 driver genes: JAK2 in approximately 60% of cases, calreticulin in approximately 20%, and myeloproliferative leukemia virus oncogene in approximately 10%.[5, 6] Mutant proteins activate the JAK/signal transducers and activators of transcription pathway and other pathways downstream, leading to myeloproliferation, proinflammatory cytokine expression, and bone marrow remodeling.[7, 8]

Because MF is associated with a heterogenous clinical phenotype, stratifying patients by prognosis can facilitate choice of appropriate treatment and identify candidates for high-risk procedures such as transplant.[9] The International Prognostic Scoring System (IPSS), used at diagnosis, utilizes 5 independent predictors of inferior survival to determine disease risk in primary MF: age >65 years, hemoglobin <10 g/dL, white cell count >25 × 10^9/L, circulating blasts ≥1%, and presence of constitutional symptoms.[10] The presence of 0, 1, 2, or ≥3 adverse features indicates low-, intermediate 1-, intermediate 2-, or high-risk disease, respectively, and corresponding median survival times range from approximately 11.3 to 2.3 years. The Dynamic International Prognostic Scoring System (DIPSS) can be used to stratify prognosis at any time during the disease course.[11] The DIPSS includes the same 5 prognostic factors as the IPSS but ascribes greater weight to low hemoglobin (2 points instead of 1); risk scoring is modified accordingly, and corresponding median survival estimates for low-, intermediate 1-, intermediate 2-, and high-risk diseases range from not reached to 1.5 years (Appendix 12). The subsequent DIPSS-Plus includes 3 additional independent prognostic factors: red blood cell (RBC) transfusion dependence, platelet count <100 × 10^9/L, and unfavorable karyotype.[12]

Until 2019, ruxolitinib, a dual JAK1/JAK2 inhibitor that was approved by the United States (US) Food and Drug Administration (FDA) in 2011 and by the European Medicines Agency in 2012, was the only available drug indicated for treatment of intermediate- and high-risk MF. Evidence suggests there may be a survival benefit with ruxolitinib compared with conventional therapies. Patients treated with ruxolitinib frequently experience gradual loss of response, have a suboptimal response or develop cytopenias during treatment, resulting in ruxolitinib discontinuation within a few months and therefore, a subsequent risk of disease rebound. In the Phase III COMFORT-I and COMFORT-II trials, pooled ruxolitinib discontinuation rates at 3 and 5 years were approximately 50% and approximately 70%, respectively. Suboptimal ruxolitinib dosing to avoid treatment-related AEs, at least initially, appears to be relatively common.[13, 14, 15, 16, 17]

Fedratinib is an oral, JAK2 inhibitor with activity against wild-type and mutationally activated JAK2 and FMS-like tyrosine kinase 3.[18] In August 2019, the US FDA approved fedratinib for treatment of adult patients with intermediate-2 or high-risk primary or secondary MF. The National Comprehensive Care Network (NCCN) clinical practice guidelines for treatment of MPNs now includes fedratinib as an option for patients with intermediate-2 or high-risk MF with platelet count ≥50 × 10^9/L, used as initial therapy or as second-line therapy for patients previously treated with ruxolitinib.[19]

Despite the benefits reported with ruxolitinib as the first-line treatment, a high proportion of patients discontinued treatment; the 1-, 2-, and 3-year discontinuation rates are 49%, 71%, and 86%, respectively.[20, 21] For patients who discontinue treatment with ruxolitinib, the median overall survival is dismal and ranges from 13 to 16 months.[22, 23] There remains a great unmet need for patients who are nonresponsive to and have discontinued treatment with a JAK inhibitor.

A detailed description of the chemistry, pharmacology, safety, and key findings of nonclinical and clinical studies for NS-018 is provided in the current Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

NS-018 is currently being developed as a therapeutic agent for MPN including MF. NS-018 has been shown to have specificity for inhibiting activated JAK2 and is expected to have a wide therapeutic range, providing a satisfactory margin of safety between its efficacy and its safety. In the Phase 2 part of the Phase 1/Phase 2 study, 15 out of 20 subjects had an SVR of 0% to 50% at Cycle 7 since baseline. One subject who had a baseline platelet count of <50,000/μL, achieved ≥35% SVR at Cycle 7. The available safety data in the Phase 1/Phase 2 study indicate an overall acceptable safety and tolerability profile for NS-018. Based on these data, NS-018 is considered to have a positive benefit-risk ratio for the treatment of subjects with MF and with platelet count of <50,000/μL.

Treatment with specific therapy such as the JAK inhibitor, ruxolitinib, was observed in minority of patients with platelets below 100,000/μL, which is in line with previous reports. Although there are case reports and series in which JAK inhibitors have been used successfully with improvement of platelet count,[24, 25] JAK inhibitors are not recommended for patients with severe thrombocytopenia according to the NCCN clinical practice guidelines for treatment of MPNs. The management of severe thrombocytopenia remains unresolved, and future studies focused on patients with low platelets are deeply needed, to extend their extremely limited treatment armamentarium. Several reports showed additional significant negative impact of severe thrombocytopenia (<50,000/μL) on prognosis of these patients,[26, 27] but little is known about the impact of severe thrombocytopenia on the outcome of patients with PMF versus post-PVMF versus post-ETMF. The fact that 1 subject with a baseline platelet count of <50,000/μL achieved ≥35% SVR at Cycle 7 of the NS-018 clinical study as well as the current clinical situation

described above, it would be worth considering that NS-018 may have a positive benefit-risk ratio for the treatment of subjects with MF with platelet count of <50,000/μL.

See Section 4.0 for details of study procedures, dose, and study design justification.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of NS-018 may be found in the IB.

3.0 OBJECTIVES AND ENDPOINTS

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of the dose of 300 mg BID of NS-018 to the BAT, in subjects with PMF, post-PVMF, or post-ETMF with severe thrombocytopenia • To compare the effect on MF-associated symptoms as measured by MF-SAF v4.0 to the BAT	• Proportion of subjects who achieve ≥35% reduction in spleen volume from baseline to Week 24 as measured by MRI (or by CT for applicable subjects) • Proportion of subjects who achieve ≥50% reduction in total symptom score from baseline to Week 24 as measured by the MF-SAF v4.0
Secondary	
• To compare the best splenic response of 300 mg BID of NS-018 to the BAT • To compare the safety of 300 mg BID of NS-018 to the BAT	• Proportion of subjects who achieve ≥35% reduction in spleen volume from baseline at any time up to Week 24 as measured by MRI (or by CT for applicable subjects) • Comparison of the safety of NS-018 versus BAT
Exploratory	
• To evaluate the effect of NS-018 on fatigue	• Improvement in fatigue as measured by (PROMIS F-SF 7b
• To evaluate the effect of NS-018 on health-related QoL and utility using the EQ-5D-5L	• Change on health-related QoL and utility using EQ-5D-5L
• To evaluate plasma PK of NS-018 in the study population	• Plasma concentration of NS-018
• To evaluate the effect of NS-018 on a bone marrow fibrosis	• Improvement of bone marrow fibrosis
• To evaluate the effect of NS-018 on phosphorylation of STAT3	• Inhibition of phospho-STAT3
• To evaluate efficacy, as measured by the rates of CR, PR, clinical improvement, SD, PD and relapse, based on the IWG-MRT response criteria	• Rates of CR, PR, clinical improvement, SD, PD and relapse as measured by the IWG-MRT response criteria
• To evaluate the effect of NS-018 on platelet • To evaluate the effect of NS-018 on RBC	• Proportion of subjects with platelet count of ≥50,000/μL at Weeks 12 and 24
• To evaluate the effect of NS-018 on transfusion	• Proportion of platelet transfusion-independent subjects at baseline with improvement in grade of thrombocytopenia at Week 24. • Proportion of transfusion-dependent subjects at baseline who achieve transfusion independence and 50% reduction in transfusion rate at Week 24 • Improvement in platelet count without transfusion at Week 24. • Rate of RBC transfusion through Week 24 (defined as the average number of RBC units/subject/month) • RBC transfusion independence rate at Week 24 • RBC transfusion dependence rate at Week 24

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
	• Improvement in hemoglobin level without transfusion at Weeks 24
• To explore changes in the expression profile of mRNA by NS-018 versus baseline assessment	• Change of mRNA expressions by using mRNA sequencing
• To evaluate the splenic response and the effect on improvement of MF-associated symptoms and fatigue up to Week 48	• Improvement in splenic response, MF-associated symptoms and fatigue up to Week 48 by NS-018
• To evaluate the splenic response and the effect on improvement of MF-associated symptoms and fatigue after transitioning from BAT to NS-018	• Improvement in splenic response, MF-associated symptoms and fatigue by NS-018 after transitioning from BAT to NS-018

Abbreviations: BAT=Best Available Therapy; BID=twice daily; CR=complete response; CT=computed tomography; ETMF=essential thrombocythemia myelofibrosis; F-SF = Fatigue Short Form; mRNA=messenger ribonucleic acid; IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; MF=myelofibrosis; MF-SAF v4.0=Myelofibrosis Symptom Assessment Form version 4.0; MRI=magnetic resonance imaging; PD=progressive disease; PMF=primary myelofibrosis; PR=partial response; PROMIS = Patient-Reported Outcomes Measurement Information System; PVMF=polycythemia vera MF; QoL=quality of life; RBC=red blood cell; SD=stable disease.

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 2b, open-label, multicenter, randomized, controlled, 2-arm study in subjects with PMF (Appendix 9), post-PVMF (Appendix 10), or post-ETMF (Appendix 11) to compare the efficacy and safety of NS-018 versus best available therapy (BAT). Subjects will be stratified at baseline by spleen volume, and by history of prior JAK inhibitor treatment, and randomized to receive either NS-018 or BAT (control group). The stratification factors will be as follows: 1) spleen volume [redacted]; 2) JAK inhibitor (naïve versus prior treatment). There will be no MF-directed treatment (other than JAK inhibitor) for at least 2 weeks prior to initiation of NS-018 or BAT. A total of 120 subjects are expected to be enrolled and randomized 1:1 to either NS-018 or BAT.

The population for this study includes male and female subjects who are 18 years of age or older with PMF, post-PVMF, or post-ETMF with severe thrombocytopenia (platelet count <50,000/μL), including subjects with DIPSS intermediate-2 or high-risk MF, and who require therapy. Subjects must have a spleen volume of at least 450 cm^3 measured by MRI (or by CT for applicable subjects) and have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 (Appendix 13) at study entry (screening). Subjects may or may not have received prior therapy for MF including JAK inhibitor.

Individual subject participation in the study will depend upon the ability to tolerate the treatment regimen and upon the time to a progression event mandating study withdrawal.

The screening period is 28 days before start of treatment. During screening, all subjects will be evaluated for active tuberculosis (except in UK). Additionally, inactive (latent) tuberculosis testing will be done in UK and South Korea by local laboratory for all subjects. At Cycle 1 Day 1, before the subject starts study treatment, all eligibility criteria including the subject's status for coronavirus disease 2019 (COVID-19) should be reviewed and confirmed. All subjects will be treated from Cycle 1 Day 1 through the end of the study. There will be an indefinite period from Cycle 7 Day 1 until the subject meets the criteria for the discontinuation of study treatment (see Section 7.1), or until 3 years (expected) after the first subject in, whichever comes first. Subjects who complete the treatment period will complete the end of study procedures within 14 days after the last dose.

Subjects who discontinue prior to completing the treatment period will be asked to complete the end of study procedures within 14 days after the last dose (see Schedule of Assessments [SoA], Section 1.3). For sites in South Korea, UK, and Germany, see SoA in Appendix 15, Appendix 16, and Appendix 17, respectively.

If the end of study procedures occurs at a regular scheduled visit, these procedures may be performed at that time.

A 30-day follow-up phone call will be scheduled after completion of the end of study procedures.

NS-018 Dosage and Mode of Administration

NS-018 will be self-administered orally at a dose of 300 mg BID. The BAT will be administered according to product label and the Investigator's discretion.

Best Available Therapy Dosage

The Investigator will decide the BAT that will be administered to the subject during the screening period based on subject's condition. The BAT must be one of the following: hydroxyurea, danazol, fedratinib, ruxolitinib, interferon, corticoid, erythropoietin, purinethol, thalidomide, lenalidomide or 'supportive care/therapy'. The BAT should be administered according to the manufacturer's instructions or the Investigator's discretion. The BAT 'supportive care/therapy', refers to use of blood products, fluids (crystalloids), pain medications, and/or antibiotics, that subjects will need to manage myelofibrosis symptoms and complications. Subjects in the control group will receive BAT at doses and schedules selected by the Investigator based on the subject's condition and according to the manufacturer's instructions or the Investigator's discretion. The BAT must be a single agent and cannot be combined with other agents. JAK inhibitor can be allowed as BAT if the JAK inhibitor was administered as a standard of care based on the product label or Investigator's discretion. The BAT may be changed at any time during the randomized treatment period based on the Investigator's clinical assessment of the subject's condition. However, it is not allowed to change the BAT to JAK inhibitor if it was not used as standard of care treatment prior to study participation. No experimental agents (ie, those not approved for any indication) may be used at any time.

Genetic Substudy

In this study, DNA/RNA testing will be conducted. In DNA testing, mutated genes are detected. The main purpose of DNA testing is to investigate a relationship between clinical benefit and genetic background. In RNA testing, an expression of mRNAs is measured. The main purpose of RNA testing is to investigate a more precise mechanism of action of NS-018 and/or explore currently unknown underlying pathophysiology of MPNs with special reference to treatment. This genetic substudy will be conducted after subjects have signed an optional genetic substudy consent form.

Study Visits

Subjects will have regular scheduled study visits at screening, Day 1 and Day 15 of Cycles 1, 2, 3, 4, 5, and 6, and Day 1 of every cycle thereafter. One cycle is 28 days. Subjects transitioning from BAT to NS-018 before or at Cycle 7 Day 1 will have safety laboratory assessments performed on Day 1 and Day 15 of each cycle for 6 cycles. Safety laboratory assessments will continue on Day 1 of the following cycles until the end of the study and will be

done by a central laboratory (refer to Appendix 17 SoA for further details). Additional local laboratory assessments may be performed per the Investigator's discretion to monitor safety and document AEs as per local standards of care.

Subjects in South Korea only, safety laboratory assessments will be performed weekly at Cycle 1 on Day 1, Day 8, Day 15, and Day 22, and Cycles 2 through 6 will be performed on Days 1 and 15, and Day 1 of each cycle thereafter. For subjects who transition to NS-018, safety laboratory assessments will be performed on Day 1 and Day 15 of each cycle for the first 6 cycles after transitioning to NS-018 (including the additional visits on Day 8 and Day 22 of the first cycle after transitioning). Laboratory visits on Day 8 and Day 22 of Cycle 1 for subjects randomized to NS-018 or Cycle 1 after transitioning to NS-018 in subjects who transition to NS-018 will be performed at the institutional local laboratory (refer to Appendix 15 for further details).

Subjects who transition from BAT to NS-018 will have a physical examination done on Day 1 of each cycle for the first 4 cycles after transitioning to NS-018 and on Day 1 of every three cycles thereafter, as subjects are transitioned to NS-018. Vital signs will be done on Day 1 of each cycle after transitioning to NS-018. Vital signs will be taken within 3 hours before transitioning to NS-018. ECG will be done on Day 1 and Day 15 of the first cycle and on Day 1 of the second and fourth cycles after transitioning to NS-018, and on Day 1 of every 3 cycles thereafter as subjects randomized to NS-018. Each ECG measurement will be performed 2 hours (±10 minutes) postdose (refer to Section 8.2.3 and Appendix 16 for further details for UK).

Subjects treated with ruxolitinib will be required to taper off ruxolitinib before initiation of NS-018 at Cycle 1 Day 1. The dose of ruxolitinib should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration of total tapering period of 14 days. Ruxolitinib should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of ruxolinitb, are already on the lowest dose possible, therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of ruxolitinib therapy) is noted, it is strongly suggested that therapy with ruxolitinib be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended.

Eligible subjects will receive NS-018 or BAT according to treatment assignment from Cycles 1 to 6 until one of the following criteria for disease progression is met:

1. Increase in spleen volume of ≥15% measured by MRI (or by CT for applicable subjects) from the baseline for subjects who are randomized to NS-018 or transitioned to NS-018.
2. Splenic irradiation or splenectomy.
3. Leukemic transformation defined by an increase in peripheral blood blast percentage to ≥20% that is sustained for at least 8 weeks.
4. Leukemic transformation defined by bone marrow blast count of ≥20%.
5. Death.

Subjects who meet the criteria for increase in spleen volume of ≥15% measured by MRI (or by CT for applicable subjects), leukemic transformation, or have had splenic irradiation will be discontinued from the study treatment and will be asked to complete the end of study procedures. Subjects randomized to the BAT arm (ie, subjects already on BAT or 'supportive care/therapy' and met all of the following criteria may transition to NS-018 treatment.

- Subject has completed at least 24 weeks on BAT or had progression of disease prior to Week 24; progression must be declared based only on an increase in splenic volume of >15% measured by MRI (or by CT for applicable subjects) from baseline.
- Subject has not undergone splenic irradiation or splenectomy.
- Subject does not meet criteria for leukemic transformation.

There will be no MF-directed treatment (other than ruxolitinib) for at least 1 week (7 days) prior to initiation of NS-018 after completion of BAT. Changes in the MF-directed treatment should be documented.

Subjects randomized to receive either NS-018 or BAT may continue to receive NS-018 after completion of Cycle 6. In the BAT treatment arm (control group), after subjects have completed treatment with BAT at the end of Cycle 6, the Investigator will determine whether subjects should continue BAT treatment outside the study (ie, withdrawn from the study) or discontinue BAT and transition to NS-018 at Cycle 7 Day 1. During this transition period, subjects treated with a ruxolitinib will be required to taper off this treatment before initiation of NS-018. The dose of ruxolitinib should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration for the total tapering period of 14 days. Ruxolitinib should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of ruxolitinib, ruxolitinib, are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of ruxolitinib therapy) is noted, it is strongly suggested that therapy with ruxolitinib be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended.

Subjects receiving treatment other than ruxolitinib will undergo a minimum washout period of 1 week (7 days) prior to start of NS-018 treatment.

For subjects receiving BAT and transitioning to NS-018 before Cycle 7 Day 1, subjects will be required to taper off or washout this treatment before initiation of NS-018 as described above.

Subjects may continue to receive treatment with NS-018 until the subject meets the criteria for discontinuation of study treatment (see Section 7.1), or until 3 years (expected) after the first subject is enrolled at any of the study centers, whichever comes first.

Visits for subjects in South Korea, UK, and Germany are detailed in a separate schedule of assessments (SoA) in Appendix 15, Appendix 16, and Appendix 17, respectively.

4.2 Scientific Rationale for Study Design

This is a Phase 2b, open-label, multicenter, randomized, controlled, 2-arm study. It will compare the efficacy and safety of NS-018 versus BAT in subjects with thrombocytopenia and primary MF, post-PVMF or post-ETMF. A total of 120 eligible subjects are expected to be randomized in a 1:1 ratio to 1 of the 2 treatment arms.

The NCCN clinical practice guidelines (2022 version 1.0) for treatment of MPNs recommends participating in clinical trial for patients with platelet counts of <50,000/μL. In this study, both JAK inhibitor-naïve patients and patients who were previously treated with JAK inhibitor can be enrolled. It is highly possible that symptoms and conditions differ very much among patients. Therefore, the BAT as comparator would be appropriate because the physician can select a treatment according to the subject's disease status.

4.3 Justification for Dose

The Maximum Tolerated Dose was not reached during the Phase 1 part of the NS-018-101 study; however, the Safety Review Committee considered the 400 mg QD and BID cohorts not tolerable based on the proportion of drug-related neurological AEs. Therefore, 300 mg BID is the maximum dose which can be administrated.

In the Phase 1 part of study NS-018-101, the best response in palpable spleen size reduction of ≥50% observed was similar between subjects administered with 300 mg QD and BID, which is 56% (5/9) and 50% (3/6), respectively. However, based on the balance of efficacy and safety results in the Phase 1 part, the 300 mg QD dose was selected as the dose for the Phase 2 part of study NS-018-101.

In the Phase 2 part of the study, SVR was measured by MRI or CT scan. There were no safety concerns in subjects administered with 300 mg QD, however, only 1 subject with a baseline platelet count of <50,000/μL achieved ≥35% reduction in spleen size volume as measured by MRI at Cycle 7.

The clinical diagnosis of splenomegaly is defined as the organ palpable below the costal margin during physical examination. However, the recognition of the spleen enlargement by means of imaging methods such as MRI or CT was proven to be more accurate and reliable and was used to measure ≥35% SVR as primary end point in pivotal study for other JAK2 inhibitors (ruxolitinib, fedratinib, and pacritinib). Based on this information, the best response in palpable spleen size reduction of ≥50% observed was similar between 300 mg QD and BID, which could have shown measurable differences with the use of MRI or CT scans. In the Phase 2 part, it was observed that subjects with higher area under the plasma concentration-time curve (AUC)

obtained higher efficacy in terms of SVR and an improvement of symptoms. This means that if SVR is measured by MRI/CT in the Phase 1 part, 300 mg BID might have had better efficacy data than 300 mg QD.

Based on the efficacy, safety, and PK data of the Phase 1/Phase 2 study NS-018-101, 300 mg BID dose of NS-018 was determined for use in this Phase 2b study NS-018-201. In case a dose reduction, dose interruption or dose re-escalation is necessary, the study treatment will be administered as described in Section 6.6.

4.4 End of Study Definition

The planned end of study is defined as the scheduled date when the last subject enrolled completes the 30-day follow-up phone call after the completion of the end of study procedures.

The total length of the study, from screening of the first subject to the 30-day follow-up phone call of the last subject, is expected to be 3 years.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Able to provide written informed consent prior to enrollment into the study.
2. Males and females ≥18 years of age.
3. Primary MF, post-PVMF or post-ETMF according to the DIPSS risk categories of intermediate-2 or high-risk MF (see Appendix 12).
4. Spleen volume of at least 450 cm^3 measured by MRI (or by CT for applicable subjects). This baseline scan will be centrally reviewed for spleen volume.
5. Total symptom score (TSS) ≥10 on MF-SAF v4.0. The TSS from the first 7 consecutive days of entry through the screening period will be used for eligibility.
6. Platelet count < 50,000/μL. Two results taken at least 7 days apart during screening are needed. Each result must be <50,000/μL.
7. No MF-directed treatment (other than ruxolitinib) for at least 2 weeks prior to initiation of NS-018, including erythropoietic, thrombopoietic agent, or any use of corticosteroids for MF symptom or blood count management. Low dose corticosteroids <10 mg/day prednisone or equivalent is allowed for non-MF purposes. Subjects treated with ruxolitinib will be required to taper off ruxolitinib before initiation of NS-018 at Cycle 1 Day 1. The dose of ruxolitinib should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration for the total tapering period of 14 days. Ruxolitinib should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of ruxolitinib are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of ruxolitinib therapy) is noted, it is strongly suggested that therapy with ruxolitinib be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended.
   Subjects who are not benefitting from ruxolitinib treatment may be enrolled in the study per the Investigator's discretion.
8. ECOG performance status ≤2.
9. QTcF ≤480 msec.
10. Peripheral blood blast count <10%.
11. Estimated creatinine clearance ≥40 mL/min/1.73 m^2 calculated using the Cockcroft and Gault equation.
12. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN) and a direct bilirubin ≤1.5 × ULN.
13. Absolute neutrophil count >500/μL.

14. Negative serum pregnancy test within 7 days prior to the first dose of study drug (if subject is a female of childbearing potential).
15. No treatment with any investigational agent within 28 days or five times the half-life of the drug prior to initiation of NS-018, whichever is longer (not shorter). COVID-19 vaccines that are commercially available or approved by local regulatory authorities and are administered outside of an investigational clinical study are not considered as investigational agents (see Section 6.5).
16. Male or non-pregnant, non-lactating female subjects. Male and female subjects who are fertile and their partners must agree to use 2 highly effective methods of contraception from screening through 180 days (for male subjects with partners who are women of childbearing potential [WOCBP], pregnant or breast feeding) and 180 days (for females) following discontinuation of study treatment as outlined in Appendix 6.

    For Germany and UK Only:
    Male or non-pregnant, non-lactating female subjects. Male and female subjects who are fertile and their partners must agree to use 2 highly effective methods of contraception from screening through 180 days for male subjects with partners who are WOCBP), pregnant or breast feeding) and 180 days for females following discontinuation of study treatment as outlined in Appendix 7.

    - Male subjects should not father a child during treatment and for 180 days thereafter.
    - Female partners must use highly effective contraceptive methods for 180 days thereafter.

    Additionally, monthly pregnancy tests should be performed for WOCBP. The serum pregnancy test should not be older than 72 hours before taking the first dose.

17. Life expectancy >6 months.

5.2 Exclusion Criteria

Subjects are excluded from study participation if any of the following criteria apply:

1. Active, uncontrolled systemic infection including active tuberculosis. Inactive (latent) tuberculosis infection testing will be done for UK and South Korea only.
2. Any prior treatment with more than 2 JAK inhibitors. Subjects with any contraindication to BAT (see the product label) are excluded.
3. Subjects receiving any clinical benefits from JAK inhibitor per the Investigator's discretion.
4. Previous treatment with NS-018. Subjects with hypersensitivity to NS-018, any excipient of NS-018 tablets and to any JAK2 inhibitor will be excluded from study participation.
5. Subjects actively receiving a concurrent investigational agent.

6. Subjects with any unresolved AE greater than Grade 1 other than hematological AEs from previous anticancer therapy.
7. Potentially curative therapy is available:
    - Candidates for hematopoietic stem cell transplant in which transplant is an available and viable option and of higher priority than this study are excluded.
    - If the subject has declined hematopoietic stem cell transplant, has no donor for transplant, or in the judgment of the Investigator is not suitable for transplant, the subject may be enrolled.
8. Currently taking medication that is substantially metabolized by cytochrome P450 (CYP) 1A2 or CYP3A4 (see Appendix 5) or taking medication known to be strong inhibitors or inducers of CYP3A4 (see Appendix 5).
9. Pregnancy or lactation.
10. Radiation therapy for splenomegaly within 6 months prior to study entry (screening).
11. History of splenectomy or planning to undergo splenectomy.
12. Known HIV positive status.
13. Known active hepatitis, or a history of viral hepatitis B or hepatitis C.
14. Subjects with a serious cardiac condition within the past 6 months such as uncontrolled arrhythmias, myocardial infarction, angina, or heart disease as defined by the New York Heart Association Class III or IV.
15. Subjects diagnosed with another malignancy within 2 years prior to an enrollment. Subjects with prior malignancies must have completed all treatments with no recurrence within 2 years to an enrollment. Subjects with an early stage squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or cervical intraepithelial neoplasia may be eligible for participation at the Investigator's discretion.
16. Subjects who have had surgery (other than placement of vascular access and bone marrow biopsy) within 4 weeks of study entry (screening), or subjects with incomplete recovery from any prior surgical procedures.
17. Other concurrent disease and/or medical condition including cardiac condition, which, in the judgment of the Investigator, would prevent the subject's participation.
18. Unwilling or unable to comply with the protocol.
19. Subjects with suspected (case definition A or B), probable, or confirmed diagnosis of COVID-19 based on the World Health Organization diagnostic criteria (Table 2).

Table 2	**World Health Organization COVID-19 Case Definition Criteria**
Suspected	**A.** A person who meets the clinical AND epidemiological criteria: Clinical criteria: 1. Acute onset of fever AND cough; **OR** 2. Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness/fatigue[a], headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status. **AND** Epidemiologic criteria: 1. Residing or working in an area with high risk of transmission of the virus: for example, closed residential settings and humanitarian settings, such as camp and camp-like settings for displaced persons, any time within the 14 days prior to symptom onset; **OR** 2. Residing in or travel to an area with community transmission[b] anytime within the 14 days prior to symptom onset; **OR** 3. Working in health setting, including within health facilities and within households, anytime within the 14 days prior to symptom onset. **B.** A patient with severe acute respiratory illness (acute respiratory infection with history of fever or measured fever of ≥38°C; and cough; with onset within the last 10 days; and who requires hospitalization).
Probable	**A.** A patient who meets clinical criteria above **AND** is a contact of a probable or confirmed case, or epidemiologically linked to a cluster of cases which has had at least 1 confirmed case identified within that cluster. **B.** A suspected case (described above) with chest imaging showing findings suggestive of COVID-19 disease* *Typical chest imaging findings suggestive of COVID-19 include the following[28]: •chest radiography: hazy opacities, often rounded in morphology, with peripheral and lower lung distribution •chest CT: multiple bilateral ground glass opacities, often rounded in morphology, with peripheral and lower lung distribution •lung ultrasound: thickened pleural lines, B lines (multifocal, discrete, or confluent), consolidative patterns with or without air bronchograms. **C.** A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause. **D.** Death, not otherwise explained, in an adult with respiratory distress preceding death **AND** who was a contact of a probable or confirmed case or epidemiologically linked to a cluster which has had at least 1 confirmed case identified within that cluster.
Confirmed	A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Source: Public health surveillance for COVID-19. Interim guidance. 07 August 2020.

Abbreviations: COVID-19=coronavirus disease 2019; CT = computerized tomography.

[a] Signs separated with slash (/) are to be counted as 1 sign.

[b] Community transmission: Countries/territories/areas experiencing larger outbreaks of local transmission defined through an assessment of factors including, but not limited to: large numbers of cases not linkable to transmission chains, large numbers of cases from sentinel lab surveillance or increasing positive tests through sentinel samples (routine systematic testing of respiratory samples from established laboratories), multiple unrelated clusters in several areas of the country/territory/area.

5.3 Lifestyle Considerations

No restrictions are required in this study.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment via the Interactive Web Response System (IWRS). A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time. Rescreened subjects should be given a new screening number and will require re-consenting. .

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol.

6.1 Study Treatment(s) Administered

The study treatment, NS-018, will be supplied by NS Pharma, Inc. NS-018 will be dispensed at Cycle 1 Day 1 (within 24 hours prior to study drug treatment) and all other applicable visits (see Section 1.3, SoA). NOTE: At Cycle 1 Day 1, before the subject starts study treatment, all eligibility criteria, including the subject's COVID-19 status, must be reviewed and confirmed.

Assigned study treatment will be administered from Cycle 1 Day 1 until the end of Cycle 6 (Table 3). After Cycle 6, subjects will be offered to receive NS-018 and continue self-administration. Subjects will be instructed not to split, crush, or chew tablets.

Subjects transitioning from BAT to NS-018 will be dispensed with NS-018 at Day 1 of every 3 cycles thereafter to meet supply requirements for the duration of the study. Subjects will continue to self-administer NS-018 until the end of the study or study discontinuation criteria is met per the Investigator's assessment.

At each visit, subjects will bring the dispensed bottles of study treatment to calculate study treatment compliance.

Table 3 Study Treatment Details

Study Treatment Name:	**NS-018**	**Best Available Therapy**
Dosage Formulation:	NS-018 is provided in [redacted] tablets. The tablet contains [redacted] mg of active NS-018 drug substance and the following inactive ingredients: [redacted]	The formulation will vary depending on BAT chosen by Investigator. Refer to product label.
Unit Dose Strength(s)/Dosage Level(s):	[redacted] mg per tablet	BAT will be administered according to product label and the Investigator's discretion.
Route of Administration:	Oral	BAT will be administered according to product label and the Investigator's discretion.

Table 3 Study Treatment Details

Study Treatment Name:	**NS-018**	**Best Available Therapy**
Dosing Instructions:	Subject will self-administer [redacted] tablets of NS-018 300 mg BID without food every day as described in the protocol. Each dose must be administered 8 to16 hours apart. The first dose will be administered while at the study center after collecting the predose PK blood sample. For purposes of accuracy, without food means taking the study treatment with water 2 hours or more after the last meal and at least 1 hour before the next meal. When the subject returns to the clinic at the next scheduled visit, any remaining study treatment (once reconciled) is discarded at the site per local procedures and subject is dispensed new bottles for the next cycle supply requirements. The returned amount should be documented on the Drug Accountability Log and kept until reconciliation is done by CRA.	BAT will be administered according to product label and the Investigator's discretion.
Packaging and Labeling:	Open-label supplies will have a label indicating the number of tablets, storage conditions, directions for use, and Sponsor study number and lot number, as well as appropriate cautionary language for the study treatment. [redacted] The labels will include space for the subject number and site/Investigator's information to be entered by the Investigator.	
Manufacturer:	NS Pharma, Inc.	The manufacturer will vary depending on BAT chosen by Investigator.

Abbreviations: BAT=Best Available Therapy; BID=twice daily; CRA=clinical research associate; PK=pharmacokinetic.

6.2 Preparation/Handling/Storage/Accountability

NS-018 tablets should be stored [redacted] in a pharmacy or a locked and secure storage facility, accessible only to those individuals authorized by the Investigator to handle the study treatment.

BAT storage requirements as described in the product insert(s) should be followed.

Maintenance of a temperature log is mandatory.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only subjects enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study treatment using the Drug Accountability Log. These logs must be available for inspection at any time. A Drug Accountability Log should also be maintained for the BAT(s) given to the subjects.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is a Phase 2b, open-label, multicenter, randomized, controlled 2-arm study. If the subject is eligible to participate in the study, the subject will be assigned to receive either NS-018 or BAT. A total of 120 subjects are expected to be enrolled into the study and randomized in a 1:1 ratio to receive either NS-018 or BAT during the treatment period (Cycle 1 to Cycle 6). Approximately 60 subjects will be randomized to receive NS-018 and approximately 60 subjects will be randomized to receive BAT.

Randomization will occur centrally by the IWRS. Randomization will be stratified by spleen volume and a history of prior JAK inhibitor treatment (naïve versus prior treatment).

Spleen volume will be assessed by the central reader who will be blinded to treatment assignments. Details of the central assessments of spleen volume will be described in an imaging review charter.

6.4 NS-018 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed, except as defined in Section 6.6. Any departures from the intended regimen must be recorded in the electronic case report form (eCRF).

Subject compliance will be monitored by assessing the tablet count from each of the dispensed bottles and returned at each visit. Subjects will complete a study treatment dosing diary that will document the time of day they took their study treatment. Tablet counts will be compared by the site to the dosing diary to further assess compliance and aid subject education regarding compliance. Documentation on the eCRF will account for subject compliance in each treatment arm. Subjects will be instructed to return any unused study treatment when attending clinic visits or if the subject is discontinued before the study is complete.

Subjects who take <80% of the expected prescribed regimen will be counseled on the importance of good compliance to the study dosing regimen. If compliance is <80% during the first month of therapy, the subject will be counseled, remain on study treatment, and will follow the study assessment schedule.

Noncompliance is defined as taking less than 80% (underdose) or more than 100% (overdose) of study treatment during any evaluation period (visit to visit). Both these situations should also be considered as protocol deviations.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken within 14 days of study drug administration will be considered a concomitant medication. The site will also enter the subject's prior therapies for MF. Subjects taking medications chronically should be maintained on the same dose and dosing schedule, if medically feasible. The product label of comparator therapies must be consulted and followed regarding concomitant therapies.

Necessary supportive measures for optimal medical care will be given throughout the study, including intravenous antibiotics to treat infections, blood components, antidiarrheals, and antiemetics. Additional care will be administered as indicated by the treating physician and the subject's medical need. No concomitant cytotoxic therapy, whether conventional or investigational, will be allowed during this study. All concomitant medications and supportive therapy must be recorded on the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

A list of excluded medications/therapy is provided in Appendix 5.

Routine prophylactic use of growth factors (granulocyte colony-stimulating factor, granulocyte macrophage-colony stimulating factor, and erythropoietin) or high dose steroids (>10 mg/day of prednisone or prednisone equivalent) is not permitted. Therapeutic use should be considered at the treating physician's discretion in subjects who develop complications secondary to cytopenias (eg, overt sepsis). This should be discussed with the Medical Monitor, if at all possible, and documented.

Blood products can be administered as needed.

The potential for drugs which are metabolized by CYP enzymes to be affected by NS-018 is considered possible. The plasma concentration of these drugs may increase or decrease when administered concomitantly with NS-018.

Subjects currently taking medication that is substantially metabolized by CYP1A2 or CYP3A4 (see Appendix 5) are not eligible for this study. Every effort should be made to change these medications to acceptable alternatives to allow subject enrollment.

Subjects taking strong CYP3A4 inducers or strong CYP3A4 inhibitors (see Appendix 5) who cannot be safely switched to an acceptable alternative are excluded from the study.

Use of moderate or weak CYP3A4 inducers or moderate or weak CYP3A4 inhibitors (see Appendix 5) is discouraged (alternative therapies should be considered) during the study, but does not disqualify the subject from study participation and does not require dose modification.

No other drugs that directly treat MF are allowed during this study. No other investigational agents and anticancer agents are permitted while on study. Herbal medications should be discontinued and not initiated while participating in the study.

Live vaccines are not allowed within 30 days prior to the first dose of study treatment and while participating in the study. In case of other type of vaccines, the subject must consult with the Investigator before vaccination. Non-live COVID-19 vaccines can be used according to the local vaccination requirements and recommendations when considered appropriate by the Investigator. Any vaccines should be recorded in the eCRF as a concomitant medication, including manufacturer, brand name, lot number if available, doses administered (first dose, second dose, etc.) with administration dates.

6.6 Dose Modification

Subjects who present the following drug-related AEs must have study treatment interrupted and a dose reduction should be considered according to Table 4:

- Grade 4 neutropenia
- Grade 4 lymphopenia
- Grade 4 thrombocytopenia with active bleeding
- Grade 3 or 4 non-hematologic AEs except for nausea, vomiting and/or diarrhea adequately controlled with standard systemic medications (per "Management of non-hematologic AEs").

Additional information about AE grades (Common Terminology Criteria for AEs [CTCAE] version 5.0) is provided in Appendix 4.

Study treatment administration may be interrupted for clinically significant AEs of ≥Grade 1 that do not meet the interruption criteria, at the discretion of the Investigator. Once the AE has resolved to Grade 0 or 1, or to baseline level within 4 weeks of study drug interruption, the study treatment may be resumed at 1 dose level below.

Subjects requiring a >4-week interruption in study treatment administration should be permanently discontinued from study participation.

If a dose reduction is necessary, the study treatment will be administered as follows (Table 4):

Table 4 Study Treatment Administration in Case of Dose Reduction

Starting dose	300 mg BID
Dose level −1	200 mg BID
Dose level −2	100 mg BID

Abbreviations: BID=twice daily.

Dose reduction would be to the next lower dose level. If the subject has been receiving starting dose, the next dose level will be level −1. If the subject has already been receiving 200 mg BID, the next dose level will be level −2. Further dose reductions are not allowed.

Dose re-escalation is permitted upon resolution to ≤Grade 1 AEs, except for hematological AEs, if deemed appropriate by the Investigator and following discussion with the medical monitoring team and Sponsor. In case of hematological AEs, dose re-escalation is determined by the Investigator and Medical Monitor.

Dose delays or modifications for BAT should occur per Investigator's discretion in accordance to approved prescribing information or institutional guidelines.

Management of non-hematologic AEs

Grade 3 or Grade 4 non-hematologic AEs will require dose interruption or dose reduction per the above guidance. For Grade 3 nausea, vomiting, and/or diarrhea should receive optimal treatment with antiemetics or antidiarrheals and persist for at least 72 hours despite the use of an optimal antiemetic or antidiarrheal regimen before being considered an AE requiring treatment interruption. The optimal antiemetic regimen is to be determined by each Investigator and should at a minimum include a 5-hydroxytrptamine ($5\text{-}HT_3$) antagonist (also called serotonin receptor antagonists or serotonin blockers). The optimal antidiarrheal regimen is to be determined by each Investigator and should at a minimum include Imodium® (loperamide hydrochloride) or Lomotil® (diphenoxylate hydrochloride and atropine sulfate).

Management of hematologic AEs

NS-018 should be held for Grade 4 neutropenia, lymphopenia, or bleeding. Treatment should be held until hematologic AE has resolved to baseline level within 4 weeks of study treatment interruption, or in a case of Grade 4 thrombocytopenia with active bleeding, until 1 week after the resolution of a bleed. Upon restart, it is additionally recommended to reduce the dose according to Table 4. If the treatment is interrupted for >4 weeks for recovery of hematologic toxicities, subjects will be permanently discontinued from the study.

Blood products can be used as needed. Use of growth factors (granulocyte colony-stimulating factor, granulocyte macrophage-colony stimulating factor, and erythropoietin) is not permitted.

6.7 Treatment after the End of the Study

The Sponsor will evaluate the appropriateness of continuing to provide the study treatment to subjects who are benefiting from treatment. Based on the benefit-risk profile, if the development of this investigational study treatment has not been discontinued and if not yet commercially available, post-study access may be provided in compliance with local regulations.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

Subjects will be permanently discontinued from the study under the following circumstances:

- Clinical progression as determined by Investigator including but not limited to the following events as described in Section 4.1:
  - Leukemic transformation defined by an increase in peripheral blood blast percentage to ≥20% that is sustained for at least 8 weeks
  - Leukemic transformation defined by bone marrow blast count of ≥20%
- Subject's physician considers a change of therapy would be in the best interest of the subject
- Death
- Continued unacceptable AEs despite optimal treatment or dose reduction (see Section 6.6)
- Need for any treatment not allowed by the protocol
- Noncompliance with study treatment and/or study procedures, as judged by the Investigator and/or Sponsor (eg, failure to return for scheduled visits, failure to complete study assessments, failure to return study treatment, etc.)
- Subjects requiring >4-week interruption in study treatment administration
- Increase in spleen volume of ≥15% measured by MRI (or by CT for applicable subjects) from the baseline for subjects who are randomized to NS-018 or transitioned to NS-018.

Subjects who are discontinued from study participation will be asked to undergo the end of study procedures within 14 days after the last dose of study treatment. If the end of study procedures occurs at a regular scheduled visit, these procedures may be performed at that time. Subjects who are discontinued will also be asked to undergo a 30-day follow-up phone call after completion of the end of study procedures (see SoA, Section 1.3). If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject must be discontinued from study treatment and the Sponsor/designee must be contacted immediately. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the subject to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor/designee to allow the subject to continue in the study.

Subjects who discontinue study treatment will not be replaced.

7.2 Subject Withdrawal from the Study

Subjects will be withdrawn from the study under the following circumstances:

- Withdrawal of consent

- Noncompliance with study treatment and/or study procedures, as judged by the Investigator and/or Sponsor (eg, failure to return for scheduled visits, failure to complete study assessments, failure to return study treatment, etc.)
- Female subjects who become pregnant during the study or who fail to use adequate birth control if applicable (refer to pregnancy section)
- Sponsor decision to terminate study.

Subjects who are withdrawn will be asked to undergo the end of study procedures within 14 days after withdrawal from the study. If the end of study procedures occurs at a regular scheduled visit, these procedures may be performed at that time. Subjects who are withdrawn from the study will also be asked to undergo a 30-day follow-up phone call after the completion of the end of study procedures (see SoA, Section 1.3). For subjects who withdraw their consent, the end of study procedures and/or the 30-day follow-up phone call will not be performed.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, the subject may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up whenever possible.

7.4 Procedures for Discontinuation in Relation to COVID-19

If a subject is diagnosed with COVID-19 or is suspected to have COVID-19 and an AE/SAE is reported (see Section 8.3.8), the Investigator should determine whether the subject's study treatment should continue, be temporarily discontinued or permanently discontinued.

Subject safety is paramount, and the Investigator should continue to reassess the risk/benefit of continued study involvement for each subject.

If a subject is unable to attend on-site visits for undergoing safety-related assessments as shown in the SoA (Section 1.3) for physical visits at study centers due to local public health rules, subject inability or subject/caregiver decision, the subject must be temporarily discontinued from study treatment, unless the safety-related assessments can be performed at the subject's home by delegated study center staff.

Such temporary discontinuation of study treatment does not mean discontinuation of follow-up. In case it is not possible to perform on-site visits, the study center staff should keep in close contact with the subject to maintain awareness of their status and on-site visits should be replaced by telephone contacts following the same procedures as detailed in the SoA (Section 1.3) for telephone visits.

If a subject is temporarily discontinued from study treatment, every effort should be made to have the subject/caregiver return all unused study treatment and empty bottles to the study center and study center staff should perform accountability as described in Section 6.2.

If this is not possible:

- Subjects should be clearly instructed that, in case of any tablets leftover in bottles already dispensed to them, they are not allowed to take the study treatment if they are not visiting the study center.
- Remaining study treatment should be returned during the first possible on-site visit.
- Reasons for not returning the study treatment and instructions given to the subject should be thoroughly documented.

According to the local public health rules and recommendations, as soon as the subject is able to undergo study protocol procedures, then the study treatment can be dispensed and treatment restarted.

If a study center is impacted by COVID-19 in a way that results in an inability to perform study activities, the study monitor should be informed as soon as possible.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Subjects will have regular scheduled study visits at screening, Day 1 and Day 15 of Cycles 1, 2, 3, 4, 5, and 6, and Day 1 of every cycle thereafter (see SoA, Section 1.3). One cycle is 28 days.

Subjects transitioning from BAT to NS-018 before or at Cycle 7 Day 1 will have safety laboratory assessments performed on Day 1 and Day 15 of each cycle for 6 cycles. Safety laboratory assessments will continue on Day 1 of the following cycles until the end of the study and will be done by a central laboratory. Additional local laboratory assessments may be performed per Investigator's discretion to monitor safety and document AEs as per local standards of care.

For subjects in South Korea only, safety laboratory assessments will be performed weekly at Cycle 1 on Day 1, Day 8, Day 15, and Day 22, and Cycles 2 through 6 will be performed on Days 1 and 15, and Day 1 of each cycle thereafter. For subjects who transition to NS-018, safety laboratory assessments will be performed on Day 1 and Day 15 of each cycle for the first 6 cycles after transitioning to NS-018 (including the additional visits on Day 8 and Day 22 of the first cycle after transitioning). Laboratory visits on Day 8 and Day 22 of Cycle 1 for subjects randomized to NS-018 or Cycle 1 after transitioning to NS-018 in subjects who transition to NS-018 will be performed at the institutional local laboratory.

Subjects who transition from BAT to NS-018 will have a physical examination done on Day 1 of each cycle for the first 4 cycles after transitioning to NS-018 and on Day 1 of every three cycles thereafter, as subjects are transitioned to NS-018. Vital signs will be done on Day 1 of each cycle after transitioning to NS-108. Vital signs taken within 3 hours before transitioning to NS-018. Subjects transitioning from BAT to NS-018 before or at Cycle 7 Day 1 will have ECG done at Cycle 7 Day 1 and will follow the same visit schedule (Cycle 7 Day 15, Cycle 8 Day 1, Cycle 10 Day 1 and thereafter Day 1 of every 3 cycles) as subjects randomized to NS-018. Each ECG measurement will be performed at 2 hours (±10 minutes) postdose.

- At Cycle 1 Day 1, before the subject starts study treatment, all eligibility criteria, including the subject's COVID-19 status, should be reviewed and confirmed.
- Study procedures and their timing are summarized in the Global SoA (Section 1.3), (Appendix 15), UK SoA (Appendix 16), and Germany SoA (Appendix 17).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will adhere to the clinical guidance of no more than 15% over an individual assessment or a weekly/monthly assessment draw. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Visits for subjects in South Korea, UK and Germany are detailed in a separate SoA in Appendix 15, Appendix 16, and Appendix 17, respectively.

8.1 Efficacy Assessments

8.1.1 Treatment Response

Treatment response will be assessed using the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) during the study at Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, and at every 3 cycles thereafter (Day 1) (see SoA, Section 1.3). The criteria are provided in Appendix 14.

8.1.2 Spleen Volume Assessment

Magnetic resonance imaging is the imaging modality of choice for the measurement of spleen volume. Subjects who have contraindications to MRI or subjects at sites where MRI is not available will be evaluated with CT scans. Both MRI and CT scans will be performed without injection of contrast material. Consistent imaging, ie, the same modality (MRI or CT) and the same technique must be used for a given individual subject throughout the study unless a new contraindication develops (such as claustrophobia) or the availability for the originally selected method is no longer possible. Spleen volume will be assessed by limited central readers who will be blinded to treatment assignments and centrally adjudicated. The full details of the central assessments of spleen volume will be described in an imaging review charter.

Spleen volume will be assessed by MRI (CT scan for subjects not able to tolerate MRI) in all randomized subjects. Spleen size measurement will be done at baseline (screening), Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and Cycle 13 Day 1. Details regarding the MRI/CT protocol will be provided in the Study Reference Manual.

Subjects transitioning to NS-018 from BAT at Cycle 7 Day 1 will also have spleen volume measurement by MRI at Cycle 7 Day 1, Cycle 10 Day 1, and Cycle 13 Day 1.

Subjects transitioning to NS-018 from BAT before Cycle 7 Day 1 (see Section 4.1, Study Visits) will have spleen volume measurement by MRI at Cycle 4 Day 1 per schedule.

8.1.3 Bone Marrow Assessment

Bone marrow assessment will be performed in subjects who are randomized to either NS-018 or BAT treatment arm. Bone marrow will be assessed by aspiration and biopsy, according to standard practice at the site at baseline (screening), Cycle 13 Day 1 and at every 12 cycles thereafter. Bone marrow assessment performed within 6 months prior to the first dose can be used as baseline

8.1.4 Myelofibrosis Symptom Assessment Form

Myelofibrosis is a highly symptomatic MPN and causes both splenomegaly-related and constitutional symptoms.[29] In addition to reducing spleen size, relieving symptom severity is a key objective of the treatment of MF.

The MF-SAF v4.0 assesses the severity of 7 core symptoms of myelofibrosis: fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety, and bone pain. The MF-SAF v4.0 asks respondents to report symptom severity at its worst for each of the 7 items on a 0 (Absent) to 10 (Worst Imaginable) numeric rating scale. The MF-SAF v4.0 is scored as a unidimensional scale to create a TSS. The TSS for the 24-hour recall (ie, daily diary) format is calculated as the sum of the 7 individual item responses on the 0 to 10 scale for a possible TSS range of 0 to 70.

The 24-hour recall (ie, daily diary) format will be used in this study. The 24-hour recall (daily diary) format asks subjects to rate the severity of each symptom at its worst during the past 24 hours (Table 5).

Table 5 Items of Myelofibrosis Symptom Assessment Form v4.0 Diary

1. During the past 24 hours, how severe was your worst fatigue (weariness, tiredness)?
2. During the past 24 hours, how severe were your worst night sweats (or feeling hot or flushed)?
3. During the past 24 hours, how severe was your worst itching?
4. During the past 24 hours, how severe was your worst abdominal discomfort (feeling pressure or bloating)?
5. During the past 24 hours, how severe was the worst pain under your ribs on your left side?
6. During the past 24 hours, what was the worst feeling of fullness you had after beginning to eat?
7. During the past 24 hours, how severe was your worst bone pain (not joint or arthritis pain)?

During the screening period, subjects will complete the MF-SAF v4.0 assessment daily. The first 7 consecutive days of diary data will be used for eligibility assessment. Subjects will complete the MF-SAF daily from Day −7 of Cycle 1 Day 1 to the end of Cycle 6 (Day 168) and the last 7 days in each cycle thereafter until the end of Cycle 12 (Day 336) for efficacy assessment.

The MF-SAF v4.0 is designed for electronic data collection by the subject and the electronic version will be used in this study.

8.1.5 Pharmacokinetics and Pharmacodynamics Assessments

The PK/pharmacodynamic assessments will be performed in subjects who are randomized to NS-018 only. Instructions for the processing, handling, and shipment of samples for central analysis will be provided in the Study Reference Manual.

8.1.5.1 Pharmacokinetics Assessments

Blood samples will be obtained for PK assessments to analyze NS-018 and its metabolite, MPD-6007. The intended time points are specified below for the study (see SoA, Section 1.3). Blood samples will be collected from subjects assigned to the NS-018 arm (60 subjects) during the randomized phase of the study at Cycles 1 and 2.

- Cycle 1 Day 1: Predose (within 1 hour) and 0.5, 1, 2, 3, 4, 6, and 8 hours (±10 minutes per time point) after administration of NS-018.
- Cycle 2 Day 1: Predose (within 1 hour) and 0.5, 1, 2, 3, 4, 6, and 8 hours (±10 minutes per time point) after administration of NS-018.

The PK parameters to be estimated include observed C_{max}, time to maximum plasma concentration (T_{max}), AUC, terminal elimination half-life ($t_{1/2}$), and accumulation ratio (AR).

8.1.5.2 Pharmacodynamic Assessments

8.1.5.2.1 Phospho-STAT3 Assessments

The intended time points for phospho-STAT3 assessments are specified below for the study (see SoA, Section 1.3).

- Cycle 1 Day 1: Predose (within 24 hours) and 3 (±10 minutes) hours after administration of NS-018.
- Cycle 2 Day 1: Predose (within 1 hour) and 3 (±10 minutes) hours after administration of NS-018.

Participation in phospho-STAT3 analysis (for NS-018 arm only) is optional and based on the site's capability to process the sample prior to shipment to the central laboratory.

8.1.5.2.2 mRNA Sequencing (optional genetic substudy)

The intended time points for mRNA sequencing are specified below for the study (see SoA, Section 1.3).

- Cycle 1 Day 1: Predose (within 24 hours) and 8 hours (±10 minutes) after administration of NS-018.
- Cycle 2 Day 1: Predose (within 1 hour).

8.1.6 Other Exploratory Assessments

8.1.6.1 Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form (F-SF) 7b

The PROMIS F-SF is a suitable measure of fatigue. The PROMIS Fatigue item banks assess a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities.

The PROMIS F-SF 7b (daily) v1.0 will be used in this study. The PROMIS 7b daily short form measures daily fatigue and asks the subject to evaluate the subject's fatigue since waking up.

The electronic version of the questionnaire must be completed daily by the subject during the screening period and the last 7 days of each cycle until the end of Cycle 12 (Day 336).[30, 31] This assessment will be performed as defined in the SoA (Section 1.3) for all subjects including subjects transitioning from BAT to NS-018.

8.1.6.2 EQ-5D-5L

The 5-level EQ-5D paper version (EQ-5D-5L; https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/) consists of 2 pages: the EQ-5D descriptive system and the EuroQoL visual analog scale (EQ VAS).

The descriptive system comprises 5 dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The subject is asked to indicate the subject's health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the subject's health state.

The EQ VAS records the subject's self-rated health on a vertical VAS, where the endpoints are labelled "The best health you can imagine" and "The worst health you can imagine." The VAS can be used as a quantitative measure of health outcome that reflect the subject's own judgement.

The EQ-5D-5L should be collected within 24 hours prior to first dose, at Cycle 7 Day 1 and every 6 cycles thereafter. The subject should complete the questionnaire before any other scheduled procedures are performed and dosing occurs.

Note: Every attempt should be made to have the questionnaires completed according to the SoA. Given the importance of having a baseline questionnaire as well as a questionnaire at end of treatment collected, if the subject discontinues treatment for reasons not due to disease

progression, questionnaires should be collected at the end of study visit (see Section 1.3 [SoA] for questionnaires to be collected).

Subjects transitioning from the BAT to NS-018 treatment before Cycle 7 Day 1 will complete the EQ-5D-5L within 24 hours prior to administering NS-018, at Cycle 7 Day 1, and every 6 cycles thereafter.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

Full physical examination, including weight and spleen size (by clinical assessment [palpation]), will be performed in accordance with the SoA (Section 1.3).

For UK only, a skin examination will also be conducted as part of the physical examination (refer to Appendix 16 for further details).

At screening, spleen size (palpation) measurement should be done on the same day the spleen volume is measured. If the same day measurement is not feasible, the measurement should be assessed within 14 days prior to the first dose of study treatment.

8.2.2 Vital Signs

The following vital signs will be assessed (within 3 hours predose) in accordance with the SoA (Section 1.3):

- Blood pressure (systolic and diastolic [mmHg])
- Heart rate (beats per minute)
- Body temperature (°C)
- Respiration rate (breaths per minute).

8.2.3 Electrocardiograms

Electrocardiogram is required for all subjects at screening. After screening, only subjects randomized to NS-018 will have ECGs done at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 4 Day 1, and Day 1 of every 3 cycles thereafter as detailed below.

- Cycle 1 Day 1: Predose (3 time points within 1 hour) and 1, 2, 4, 6, 8 (±10 minutes) hours after administration of NS-018
- Cycle 1 Day 15: 2 (±10 minutes) hours after administration of NS-018.
- Cycle 2 Day 1: Predose (within 1 hour) and 1, 2, 4 (±10 minutes) hours after administration of NS-018
- Cycle 4 Day 1 and thereafter every 3 cycles: 2 (±10 minutes) hours after administration of NS-018

For UK only, ECGs Cycle 1 Day 1: predose (3 time points within 1 hour) and 1, 2, 4, 6, 8 (±10 minutes) hours after administration of NS-018, Cycle 1 Day 15: 2 (±10 minutes) hours after administration of NS-018, Cycle 2 Day 1: predose (within 1 hour) and 1, 2, 4 (±10 minutes) hours after administration of NS-018, Cycle 3 Day 1 predose (within 1 hour) and 1, 2, and 4 (±10 minutes) hours after administration of NS-018, and Cycle 4 Day 1 and thereafter every 3 cycles: 2 (±10 minutes) hours after administration of NS-018. NOTE: An additional single ECG will be done at Cycle 3 and Cycle 9, Day 1 predose (within 1 hour) and 1, 2, and 4 (±10 minutes) hours after administration of NS-018 . Refer to Appendix 16 for UK SoA for further details.

- At screening, ECG will be used for eligibility determination and centrally read for all subjects. Median QTcF must be ≤480 msec.
- Triplicate (for screening, Cycle 1 and Cycle 2) and single and Cycle 4 and thereafter) 12-lead ECG (central read) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.
- At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

When time points for ECG measurements coincide with the time points for PK sampling, triplicate ECG collection should take place immediately prior to the collection of the plasma sample for PK.

All ECGs will be read centrally. If actions are triggered based on local read by the Investigator/study center they should be documented in source documents and corresponding eCRF sections. Details regarding the ECG collection and reading will be provided in the Study Reference Manual.

Subjects transitioning from BAT to NS-018 before or at Cycle 7 Day 1 will have ECG done on Day 1 and Day 15 of the first cycle of NS-018, Day 1 of the second and fourth cycles, and on Day 1 of every three cycles thereafter as subjects randomized to NS-018. Each ECG measurement will be performed at 2 hours (±10 minutes) postdose.

8.2.4 Clinical Safety Laboratory Assessments

Safety laboratory assessments (hematology, chemistry, and urinalysis) will be performed for both BAT and NS-018 treatment arms by a central laboratory by means of their established methods. Additional local laboratory assessments may be performed per Investigator's discretion to monitor safety and document AEs as per local standards of care. Before starting the study, the Investigator will supply the Sponsor with a list of the normal ranges and units of measurement.

Subjects transitioning from BAT to NS-018 will have safety laboratory assessments performed on Day 1 and Day 15 of each cycle for 6 cycles. Safety laboratory assessments will continue on Day 1 of the following cycles until the end of the study and will be done by a central laboratory (refer to Section 1.3 and Appendix 16 SoA for further details). Additional local laboratory assessments may be performed at the Investigator's discretion to monitor safety and document AEs as per local standards of care.

Subjects in South Korea only, safety laboratory assessments will be performed weekly at Cycle 1 on Day 1, Day 8, Day 15, and Day 22, and Cycles 2 through 6 will be performed on Days 1 and 15, and Day 1 of each cycle thereafter. For subjects who transition to NS-018, safety laboratory assessments will be performed on Day 1 and Day 15 of each cycle for the first 6 cycles after transitioning to NS-018 (including the additional visits on Day 8 and Day 22 of the first cycle after transitioning). Laboratory visits on Day 8 and Day 22 of Cycle 1 for subjects randomized to NS-018 or Cycle 1 after transitioning to NS-018 in subjects who transition to NS-018 will be performed at the institutional local laboratory. Visits for subjects in South Korea are detailed in a separate SoA in Appendix 15.

- See Appendix 3 for the list of clinical laboratory tests to be performed (refer to the SoA for the timing and frequency).
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs/SAEs. All AEs/SAEs, whether related or not, should be followed until resolution or until 30 days post close of the study.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs, including SAEs, will be collected from the signing of the informed consent form (ICF) at the time points specified in the SoA (Section 1.3). All preexisting medical conditions that are present prior to signing the ICF should be documented as part of the medical history.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and serious or nonserious AEs of special interest (AESIs as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4. Following the 30-day window after last dose of study drug, only SAEs and AESIs considered as related/ potentially related to study drug should be reported.

8.3.4 Regulatory Reporting Requirements for SAEs

- Notification by the Investigator to the Sponsor/designee of an SAE within 24 hours is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The Sponsor/designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor/designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor/designee policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor/designee will review and document the review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study treatment.

The Investigator must follow the pregnancy either to term or termination and will collect data on both maternal and fetal outcomes until final outcome (ie, normal, abnormal including abortion). Pregnancy alone is not considered an AE.

If pregnancy is reported, the Investigator should inform the Sponsor/designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

The AESIs for this study may include bleeding of any grade, cardiac events of any grade, non-melanoma skin cancer, opportunistic infections such as herpes zoster, progressive multifocal encephalopathy, and tuberculosis. Any development of tuberculosis will be recorded as an AESI.

The AESIs should be promptly recorded in the eCRF so that the Independent Data Monitoring Committee (IDMC) and Medical Monitor are notified. Such events will be reviewed and documented by the IDMC and Medical Monitor to enable consideration of implications for other subjects.

The AESIs that qualify as SAEs should be reported according to Section 8.3.4 and Appendix 4.

8.3.7 Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Events of progression of the underlying MF and events clearly related to the progression of the MF should not be reported as an AE or SAE. These events will be recorded on the corresponding eCRF page in the subject's eCRF.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE or SAE if it meets the serious criteria:

- *The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject.*
  OR
- *The Investigator considers that there is a reasonable possibility that the event was related to study treatment.*

Other events not considered SAEs for the purpose of this protocol are:

- Overdose of study drug or concomitant medication unless associated with an SAE. Note that these should be captured as an AE in the corresponding eCRF page.
- Preplanned or elective hospitalization including social and/or convenience situations.
- Hospital visits of less than 24 hours of duration which do not result in hospitalization.

8.3.8 Procedures in Relation to COVID-19 Infection

If a subject presents with clinical signs and symptoms consistent with COVID-19 infection, the Investigator should request a test where possible and this should be recorded in the AE field of the eCRF as follows:

- If test is positive, record as "COVID-19 confirmed".
- If test is negative, record the AE/SAE signs and symptoms and/or other diagnosis.
- If test is not available and signs and symptoms, as judged by the Investigator, are highly suspicious of COVID-19 infection, record as "COVID-19 suspected".

If other concurrent diagnoses exist, eg, pneumonia, the Investigator should record as separate AEs.

If an AE/SAE is associated with COVID-19, the Investigator should determine whether the subject's treatment should continue, be temporarily interrupted, or permanently stopped. Refer to Section 7.4 for discontinuation procedures in relation to COVID-19.

All AE reporting instructions in this section and SAE reporting in Section 8.3 also apply to any AE/SAE associated with COVID-19.

8.4 Treatment of Overdose

For this study, any dose of NS-018 greater than 300 mg BID within a 24-hour time period will be considered an overdose. For BAT, refer to the approved label/package insert for overdose information.

The Sponsor does not recommend a specific treatment for an overdose. In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 2 days).
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study treatment if possible and requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.5 Pharmacokinetics

The PK parameters will include:

Cycle 1 Day 1

- C_{max}
- T_{max}
- Area under the plasma concentration-time curve (AUC_{0-24})
- Terminal elimination phase rate constant (λz)
- $t_{½}$
- Apparent total body clearance (CL/F)
- Apparent volume of distribution (Vz/F)
- Lag time (T_{lag})

Cycle 2 Day 1

- C_{max}
- T_{max}
- AUC_{0-24}
- λz
- $t_{½}$
- AR = [AUC_{0-24}] Cycle 2 Day 1/[AUC_{0-24}] Cycle 1 Day 1
- Average plasma concentration (C_{av})

- Observed minimum plasma concentration (C_{min})
- Percentage fluctuation
- PTF % =100 × (C_{max} − C_{min})/C_{av}
- CL/F
- Vz/F
- T_{lag}
- Whole blood samples of approximately 3 mL will be collected from subjects assigned to the NS-018 treatment arm only for measurement of plasma concentrations of NS-018 and MPD-6007 as specified in the SoA (Section 1.3). A maximum of 8 samples may be collected including sample taken predose and samples taken at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose. Instructions for the collection and handling of biological samples will be provided by the Sponsor/designee. The actual date and time (24-hour clock time) of each sample will be recorded. The time and date of study treatment administration and the subject's most recent ingestion of drugs will also be recorded.
- Samples will be used to evaluate the PK of NS-018 and MPD-6007. Each plasma sample will be divided into 5 aliquots (for 2 primary PK samples and 3 back-up PK samples). Analyses of NS-018 and MPD-6007 plasma concentration may also be used to evaluate safety, efficacy or PK aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained. At visits during which plasma samples for the determination of NS-018 will be taken, 1 sample of sufficient volume can be used.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor/designee and study center study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

If a subject refuses blood collection for PK analysis, this will not be considered a protocol violation as the PK analysis is a secondary objective.

8.6 Pharmacodynamics

Venous blood samples will be collected for measurement of phospho-STAT3 assessments, and mRNA sequencing at the time points specified in the SoA (Section 1.3). Details on processes for collection and shipment of these samples can be found in the study laboratory manual.

8.7 Genetics

Blood samples for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study. Sample for genetic testing can be

collected at any time prior to first dose at Cycle 1 Day 1. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 7 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the study laboratory manual.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health Economics/Medical Resource Utilization and Health Economics

Not applicable.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

All statistical tests will be performed at a significance level of 0.05 with no corrections for multiple comparisons.

The first primary endpoint is the proportion of subjects who achieve ≥35% SVR from baseline to Week 24 (splenic response). The null hypothesis (H_0) and the alternative hypothesis (H_A) are:

> H_0: The null hypothesis is that the proportion of subjects who achieve ≥35% SVR from baseline to Week 24 in each treatment arm is the same.
>
> H_A: The alternative hypothesis is that the proportion of subjects who achieve ≥35% SVR from baseline to Week 24 is different by treatment arm.

The second primary endpoint is the proportion of subjects who achieve ≥50% reduction in TSS from baseline to Week 24 as measured by MF-SAF v4.0. The null hypothesis (H_0) and the alternative hypothesis (H_A) are:

> H_0: The null hypothesis is that the proportion of subjects who achieve ≥50% reduction in TSS from baseline to Week 24 as measured by MF-SAF v4.0 in each treatment arm is the same.
>
> H_A: The alternative hypothesis is that the proportion of subjects who achieve ≥50% reduction in TSS from baseline to Week 24 as measured by MF-SAF v4.0 is different by treatment arm.

The efficacy of SVR and TSS, as co-primary endpoints, will be confirmed when the null hypotheses of SVR and TSS are rejected simultaneously.

9.2 Sample Size Determination

A total of 120 randomized subjects (60 subjects in each treatment arm) is planned. The sample size determination is based on literature.[32, 33]

Assuming a splenic response rate of 20% in the NS-018 arm and 1% in the BAT arm, there is 93.5% power at the final analysis to maintain a type I error rate of 5% (ie, a 2-sided significance level using Fisher's exact test is 5%). Similarly, assuming a symptom response rate of 33% in the NS-018 arm and 8% in the BAT arm, the power of the final analysis to maintain a Type I error rate of 5% is 91.0%. Assuming that there is no correlation between SVR and TSS reduction, the power to reject the null hypothesis for both endpoints is 85.1%.

9.3 Populations for Analyses

The intent-to-treat (ITT) population will consist of all randomized subjects.

The modified intent-to-treat (mITT) population will consist of all randomized subjects who receive at least 1 dose of study treatment and have a baseline assessment and at least 1 postbaseline efficacy assessment. Subjects will be analyzed as randomized. This will be the primary analysis population for the evaluation of efficacy.

The safety (SAF) population will consist of all randomized subjects who receive at least 1 dose of study treatment. For BAT subjects who do not receive therapy, a Cycle 1 Day 1 visit is required to be included in the SAF. Subjects will be analyzed as treated. This will be the primary analysis population for the evaluation of exposure and safety.

A second safety (SAF2) population will consist of subjects randomized to BAT who complete BAT through 6 cycles and go on to receive at least 1 dose of NS-018. Baseline will consist of the last data available prior to initiation of NS-018.

The PK concentration population will consist of all randomized subjects who received at least 1 dose of study treatment and have at least 1 plasma concentration value for study treatment.

9.4 Statistical Analyses

A more technical and detailed description of the statistical methods will be provided in the statistical analysis plan (SAP). The SAP will be developed and finalized before database lock and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy Analyses

The primary efficacy analyses will be performed on the mITT population (Table 6). Efficacy data from the SAF2 population will be presented separately.

Table 6 Efficacy Analyses	
Endpoint	**Statistical Analysis Methods**
First Primary	The first primary endpoint of a proportion of subjects who achieve ≥35% SVR from baseline to Week 24 will be compared between the NS-018 group and the BAT group using Firth-corrected logistic regression model. Covariates of baseline spleen volume and a history of prior JAK inhibitor treatment will be included. Model-based point estimates for the treatment effects, 95% confidence intervals, and p-values will be calculated. Subjects who do not reach Week 24 will be considered treatment nonresponders (ie, did not achieve ≥35% SVR from baseline to Week 24). No imputations will be made for missing data. Subgroup analyses may be performed by age, gender, race, stratification factors and other baseline characteristics. The primary efficacy analyses will be conducted after all subjects have completed assessments at Week 24 (Cycle 7 Day 1).
Second Primary	Similar to the analysis of the first primary endpoint, the second primary endpoint of proportion of subjects who achieve ≥50% reduction in TSS from baseline to Week 24 as measured by MF-SAF v4.0 will be compared between the NS-018 group and the BAT group using Firth-corrected logistic regression model. Covariates of baseline spleen volume and a history of prior JAK inhibitor treatment will be included.
Secondary	Similar to the analysis of the primary endpoint, the secondary endpoint of proportion of subjects who achieve ≥35% SVR any time up to Week 24 will be compared between the NS-018 group and the BAT group using Firth-corrected logistic regression model. Covariates of baseline spleen volume and a history of prior JAK inhibitor treatment will be included.
Exploratory	Will be described in the SAP finalized before database lock.

Abbreviations: BAT=Best Available Therapy; JAK=Janus kinase; MF-SAF v4.0=Myelofibrosis Symptom Assessment Form version 4.0; SAP=statistical analysis plan; SVR=spleen volume reduction; TSS=total symptom score.

The primary estimand is defined as:

- **Population of interest**: Subjects with PMF, post-PVMF, or post-ETMF with severe thrombocytopenia defined by the inclusion/exclusion criteria.
- **Variables/endpoints of interest**:
  - Proportion of subjects who achieve ≥35% SVR from baseline to Week 24.
  - Proportion of subjects who achieve ≥50% reduction in TSS from baseline to Week 24 as measured by MF-SAF v4.0.
- **Intercurrent event handling strategy**:
  - Death due to any cause: Subject death for any cause occurring prior to Week 24 will be considered as a non-response for the first and second primary endpoint definitions (ie, did not achieve ≥35% SVR from baseline to Week 24 and did not achieve ≥50% reduction in TSS from baseline to Week 24, respectively).
  - Prohibited medication: Subjects who take prohibited medication during the study will be analyzed by the treatment policy strategy, ie, data collected after the initiation of prohibited medications will be included in analysis as collected.

- **Population-level summary measure**:
  - Difference in proportion of subjects achieving ≥35% SVR from baseline to Week 24 between the NS-018 group and the BAT group will be analyzed as described in Table 6.
  - Difference in proportion of subjects who achieve ≥50% reduction in TSS from baseline to Week 24 as measured by MF-SAF v4.0 between the NS-018 group and the BAT group will be analyzed as described in Table 6.

The following sensitivity analysis will be planned for the primary estimand:

- In the mITT population, subjects who experience death prior to Week 24, the last SVR will be imputed to Week 24 for the first primary endpoint.

The following supplementary analysis will be planned for the primary estimand:

- A per-protocol analysis consisting of all subjects without a major protocol violation that might affect the efficacy assessment (criteria will be specified prior to unblinding), following the same method as described for the primary estimand.

Additional sensitivity and supplementary analysis will be explored in the SAP as appropriate.

A similar intercurrent event handling strategy will be used for estimands related to the second primary endpoint of proportion of subjects who achieve ≥50% reduction in TSS from baseline to Week 24 as measured by MF-SAF v4.0 and the secondary endpoint of proportion of subjects who achieve ≥35% SVR any time up to Week 24.

9.4.2 Safety Analyses

The primary safety analyses will be performed on the SAF population. Safety data from the SAF2 population will be presented separately.

Adverse Events

Treatment-emergent AEs are defined as AEs that first occurred or worsened in severity after the first administration of study treatment and up to 30 days after the last administration of study treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. For each study treatment, numbers of TEAEs and incidence rates will be tabulated by preferred term and system organ class.

Treatment-emergent AEs by maximum severity, TEAEs by relationship to study treatment, AESIs, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated for each treatment group.

All central and local laboratory test results, vital signs measurements, ECG results, physical examination, spleen size (by palpation), spleen volume (by MRI) and weight will be summarized for each treatment group using descriptive statistics at each visit for raw numbers and change from baseline.

9.4.3 Other Analyses

All analyses, summaries, and listings will be performed using SAS® software (version 9.4 or higher). If not stated otherwise, all efficacy data will be summarized descriptively by treatment group and visit.

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: sample size (n), mean, standard deviation, median, minimum (min), and maximum (max).
- Categorical variables: frequencies and percentages.

Individual subject data will be presented in listings.

Pharmacokinetics, pharmacodynamics, and exploratory analyses will be described in the SAP finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

9.4.3.1 Pharmacokinetics Analyses

Blood samples for PK analysis of NS-018 will be collected at the designated study visits. All PK analyses will be based on the PK population.

Plasma concentrations of NS-018 will be summarized descriptively by time point of collection. Summary statistics including number of subjects, arithmetic mean, geometric mean, geometric coefficient of variation, coefficient of variation, standard deviation, minimum, maximum, median, and standard error of the mean will be presented. Individual subject and mean plasma concentrations of NS-018 will be plotted versus time in linear and log-linear scale.

Derived PK parameters will be listed and summarized using the same measures as for the plasma concentrations of NS-018.

9.4.3.2 Pharmacodynamic Analyses

The pharmacodynamic analysis for phospho-STAT3 will be based on the pharmacodynamic population. Phospho-STAT3 values at each time point and changes from baseline will be summarized descriptively and listed.

9.4.4 Missing Data

Data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the analyses of primary and secondary outcomes.

Sensitivity analyses of the primary endpoints to assess the impact of missing data and any imputation methods for secondary efficacy endpoints and partially missing dates will be described in the SAP.

9.5 Interim Analyses

No interim analysis is planned for efficacy. The primary efficacy analyses will be conducted after all subjects have completed assessments at Week 24 (Cycle 7 Day 1). A final analysis will be conducted at the end of the study. An additional analysis for futility may also be performed. The SAP will describe these analyses in greater detail.

9.6 Independent Data Monitoring Committee

An IDMC will be set up to oversee safety across the life span of the study and all specifics will be captured in the IDMC charter.

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
λz	terminal elimination phase rate constant
ADL	activities of daily living
AESI	adverse event of special interest
AE	adverse event
ALT	alanine aminotransferase
AR	accumulation ratio
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24
BAT	best available therapy
BID	twice daily (“bis in die” Latin)
C_{av}	average plasma concentration
CI	clinical improvement
CL/F	apparent total body clearance
C_{max}	maximum concentration
C_{min}	observed minimum plasma concentration
CR	complete response
COVID-19	coronavirus disease 2019
CRF	case report form
eCRF	electronic case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DIPSS	Dynamic International Prognostic Scoring System
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMH	extramedullary hematopoiesis
ELN	European leukemiaNet
EQ VAS	EuroQoL Visual Analog Scale

Abbreviation	Definition
ETMF	essential thrombocythemia myelofibrosis
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
F-SF	fatigue short form
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
ITT	intent-to-treat
mITT	modified intent-to-treat
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
IWRS	interactive web response system
JAK	Janus kinase
mRNA	messenger ribonucleic acid
MF	myelofibrosis
MF-SAF v4.0	Myelofibrosis Symptom Assessment Form version 4.0
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Care Network
PD	progressive disease
PK	pharmacokinetics
PMF	primary myelofibrosis
PR	partial response
PROMIS	Patient-Reported Outcomes Measurement Information System
PVMF	polycythemia vera myelofibrosis

Abbreviation	Definition
QD	once daily
QoL	quality of life
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAF	safety
SAF2	second safety
SAP	statistical analysis plan
SoA	Schedule of Assessments
SRC	Safety Review Committee
STAT3	signal transducer and activator of transcription (3)
SUSAR	suspected unexpected serious adverse reactions
SVR	spleen volume reduction
TEAE	treatment-emergent adverse event
T_{lag}	lag time
T_{max}	time to maximum plasma concentration
$T_{½}$	terminal elimination half-life
TSS	total symptom score
UK	United Kingdom
ULN	upper limit of normal
US	United States
Vz/F	apparent volume of distribution
WHO	World Health Organization
WOCBP	women of childbearing potential
Terms	**Definition**
BAT ‘supportive care/therapy’	Refers to use of blood products, fluids (crystalloids), pain medications, and/or antibiotics, that subjects will need to manage myelofibrosis symptoms and complications.

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 19). The study will not start at any study center at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

A subject who is rescreened will be required to sign another ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor/designee. Any subject records or datasets that are transferred to the Sponsor/designee will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor/designee in accordance with local data protection law. The level of disclosure must also be explained to the subject.

- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor/designee, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.
- The Sponsor/designee or its representative will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, the Sponsor/designee or representative physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

Administrative Structure

Table 7 Study Administrative Structure

Function	Responsible Organization
Study Operations Management Medical Monitoring	IQVIA Biotech
Study Master File	IQVIA Biotech
Randomization Code	Cenduit: IRT (Interactive Web Response System)
Data Management	IQVIA Biotech
Clinical Supply Management	Alcura
Quality Assurance Auditing	IQVIA Biotech
Biostatistics Medical Writing	IQVIA Biotech
Electronic Clinical Outcome Assessment	Signant Health
Imaging (Magnetic Resonance Imaging)	Clario (formerly Bioclinica)
Laboratory Assessments	Q2 Solutions
Electrocardiogram Collection, Review, and Analysis	Clario (formerly ERT)
Pharmacokinetic Sample Testing	Sumika Chemical Analysis
Safety Monitoring Committee (see Section 9.6)	IQVIA Biotech
pSTAT3 Assessment	Cerba
mRNA	Takara-Bio

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the EU database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 10 years after the last approval of a marketing application in an ICH region unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The

Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Clinical Monitoring Plan.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.
- Unjustifiable risk and/or toxicity in risk-benefit analysis (decision taken by sponsor representative), eg, when adverse events occur, unknown to date in respect of their nature, severity, duration or frequency in relation to the current established safety profile (substantial changes in risk-benefit considerations), and therefore medical and/or ethical reasons affect the continued performance of the study.
- New scientific evidence becomes available during the study that could affect the subject's safety (benefit-risk analysis no longer positive), eg, new insights from other clinical trials.
- Request of the sponsor or regulatory agency, eg, as a consequence of inspection.
- In case of difficulties in the recruitment of the planned number of subjects in the indicated time (insufficient recruitment rate).
- Withdrawal of the license to manufacture.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

Appendix 3 Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the central laboratory.
- For South Korea, the tests detailed in Table 8 will be performed by the central laboratory at all timepoints, except for the assessments on Day 8 and Day 22 of the first cycle (or the first cycle after transition to NS-018), which will be performed in the local laboratory.
- For South Korea and UK, the screening test for latent tuberculosis will be performed in the institutional local laboratory.
- Additional local laboratory assessments may be performed per Investigator's discretion to monitor safety and document AEs as per local standards of care.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator, local standard of care, or required by local regulations.

Table 8 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH)	White Blood Cell Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total protein
	Glucose (nonfasting)	Chloride	Alkaline phosphatase	Lactate dehydrogenase
	Albumin	Magnesium	Amylase	Lipase
	Uric acid			
Routine Urinalysis[a]	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, nitrite by dipstick • Microscopic examination (if blood or protein is abnormal)			

Table 8	**Protocol-required Safety Laboratory Assessments**
Laboratory Assessments	**Parameters**
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[a] • Serology (human immunodeficiency virus [HIV] antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Active tuberculosis and country-specific requirement in South Korea and UK only: Inactive (latent) tuberculosis test (local laboratory) The results of each test must be entered into the (e)CRF.
NOTES: [a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.	

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Hospital visits of less than 24 hours of duration which do not result in hospitalization. • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor/designee in lieu of completion of the CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor/designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf) or higher grading scale. For AEs not covered by National Cancer Institute (NCI) CTCAE, the severity will be characterized as mild, moderate, severe, life-threatening, or fatal according to the following definitions:

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

A semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated, unlikely to be related, possibly related, probably related, or definitely related.
    - "Definitely related" conveys the adverse event has a timely relationship to administration of study treatment and there is no apparent, potential alternate etiology.
    - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
    - "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
    - "Unlikely to be related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
    - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor/designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
    - Events deemed "Unlikely to be related" and "Unrelated" will not be considered a SUSAR for regulatory reporting purposes.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor/designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to the Sponsor/designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to Sponsor/designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Sponsor/designee will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool (see next section). • The study center will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a study center receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) or to the Medical Monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found in the Investigator Study Binder

SAE Reporting to Sponsor/designee via Paper CRF
• E-mail transmission of the SAE paper CRF is the preferred method to transmit this information to Sponsor/designee with Facsimile transmission as back-up method. • In rare circumstances and in the absence of e-mail/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the Investigator Study Binder. Submission of paper CRF pages, in the event electronic data collection tool is unavailable, should be completed and submitted via e-mail to Safety-Inbox.Biotech@IQVIA.com or faxed to +1-919-313-1412.

Appendix 5 Excluded Medications/Therapy

Excluded medications/therapy is listed below. The use of an excluded medication/therapy is a protocol violation and must be recorded in the eCRF.

The tables below list many of the medications that are prohibited or cautioned. See the website (http://medicine.iupui.edu/clinpharm/ddis/table.asp) for additional medications that may not be listed.

CYP1A2 and CYP3A4 Substrates (Drugs Substantially Metabolized by CYP1A2 or CYP3A4) Use of these drugs is prohibited	
CYP1A2 Substrates	
amitriptyline	ondansetron
excessive caffeine	phenacetin
clomipramine	propranolol
clozapine	riluzole
cyclobenzaprine	ropivacaine
duloxetine	tacrine
estradiol	theophylline
fluvoxamine	tizanidine
haloperidol	triamterene
imipramine N-DeMe	verapamil
mexiletine	warfarin
naproxen	zileuton
olanzapine	zolmitriptan
CYP3A4 Substrates	
Macrolide antibiotics including clarithromycin, erythromycin and telithromycin (not azithromycin)	
Benzodiazepines including alprazolam, diazepam, midazolam, and triazolam	
Immune modulators including cyclosporine and tacrolimus	
Antihistamines including astemizole and chlorpheniramine.	
Calcium channel blockers including amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil	
HMG CoA reductase inhibitors (Statins) including atorvastatin, cerivastatin, lovastatin, simvastatin (not pravastatin and rosuvastatin)	

Steroid 6beta-OH including estradiol, hydrocortisone, progesterone, and testosterone		
Miscellaneous:		
alfentanil	eplerenone	quinidine
aprepitant	fentanyl	quinine
aripiprazole	finasteride	risperidone
buspirone	haloperidol	salmeterol
cafergot	LAAM	sildenafil
excessive caffeine	lidocaine	sirolimus
cilostazol	methadone	tamoxifen
cocaine	nateglinide	trazodone
codeine N-demethylation	ondansetron	zaleplon
dexamethasone	pimozide	ziprasidone
dextromethorphan	propranolol	zolpidem
domperidone	quetiapine	

CYP3A4 STRONG Inhibitors and Inducers **Use of these drugs is prohibited**	
CYP3A4 Inhibitors	**CYP3A4 Inducers**
clarithromycin itraconazole ketoconazole nefazodone telithromycin	rifampin St. John's Wort
CYP3A4 MODERATE Inhibitors and Inducers Use of these drugs is discouraged (alternative therapies should be considered) but does notdisqualify subject participation in the study.	
CYP3A4 Inhibitors	**CYP3A4 Inducers**
aprepitant diltiazem erythromycin fluconazole grapefruit juice verapamil	carbamazepine phenobarbital phenytoin pioglitazone rifabutin troglitazone

Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
   a. Documented hysterectomy.
   b. Documented bilateral salpingectomy.
   c. Documented bilateral oophorectomy.
      Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b. Females on HRT and whose menopausal status is in doubt will be required to use highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects must refrain from donating sperm for the duration of the study and for 180 days after study completion or the last dose of study treatment.
- Male subjects with partners who are WOCBP, pregnant or breastfeeding must agree to remain abstinent from penile-vaginal intercourse throughout the study treatment period until 180 days from last study treatment.
- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

The following are not acceptable methods of contraception:

- Periodic abstinence (calendar, symptom-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
- Male condom with cap, diaphragm or sponge with spermicide.
- Male and female condom cannot be used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use 2 highly effective methods of contraception consistently and correctly as described in the table below. Female subjects must use the permitted contraception during the study and for 180 days after the last dose of NS-018 or for the duration required by product information of the comparator drug. Contraception requirements in the product information of a comparator therapy must be followed.

Highly Effective Contraceptive Methods

Highly Effective Methods That Are User Independent [a]
• Intrauterine device. • Intrauterine hormone-releasing system (Italy only). • Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Failure rate of less than 1% per year. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. Two highly effective methods of contraception should be utilized during the treatment period and for 180 days (for females) and 180 days (for male subjects with partners who are women of childbearing potential [WOCBP], pregnant or breast feeding), corresponding to time needed to eliminate study treatments with genotoxic potential after the last dose of study treatment. Hormonal contraception methods are not allowed to be used.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at times specified in the SoA (Section 1.3).

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor/designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor/designee. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor/designee within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor.
- The Investigator must follow the pregnancy either to term or termination and will collect data on both maternal and fetal outcomes until final outcome (ie, normal, abnormal including abortion). Pregnancy alone is not considered an AE.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor/designee as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

Appendix 7 Contraceptive Guidance and Collection of Pregnancy Information for Germany and United Kingdom

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with one of the following:
   a. Documented hysterectomy.
   b. Documented bilateral salpingectomy.
   c. Documented bilateral oophorectomy.
      Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b. Females on HRT and whose menopausal status is in doubt will be required to use 2 highly effective contraception methods as described in the table below if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- In addition, male subjects must refrain from donating sperm for the duration of the study and for 180 days after study completion or the last dose of study treatment.
  Male subjects with partners who are WOCBP, pregnant or breastfeeding must agree to remain abstinent from penile-vaginal intercourse throughout the study treatment period until 180 days from last study treatment.

  For UK only: Male subjects must use a condom during sexual intercourse with a female partner who is WOCBP during the study and for 180 days after the last dose of NS-018 or for the duration required by product information of the comparator drug.

Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use 2 highly effective methods of contraception consistently and correctly as described in the table below. Female subjects must use the permitted contraception during the study and for 180 days after the last dose of NS-018 or for the duration required by product information of the comparator drug. Contraception requirements in the product information of a comparator therapy must be followed.

For UK only, female subjects must use the permitted contraception during the study and for 180 days after the last dose of NS-018 as per Appendix 7 guidance for females, or for the duration required by product information of the comparator drug.

The following are not acceptable methods of contraception:

- Periodic abstinence (calendar, symptom-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
- Male condom with cap, diaphragm or sponge with spermicide.
- Male and female condom cannot be used together.

Highly Effective Contraceptive Methods

Highly Effective Methods That Are User Independent [a]
• Intrauterine device. • Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Failure rate of less than 1% per year. Typical use failure rates may differ from those when used consistently and correctly.

Two highly effective methods of contraception should be utilized during the treatment period and for 180 days (for females) and 180 days (for male subjects with partners who are women of childbearing potential [WOCBP], pregnant or breast feeding), corresponding to time needed to eliminate study treatments with genotoxic potential after the last dose of study treatment or for the duration required by product information of the comparator drug. Hormonal contraception methods are not allowed to be used.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at times specified in the SoA (Appendix 16 and Appendix 17).
- A negative serum pregnancy test will be required within 7 days prior to dosing on Cycle 1 Day 1, and a negative urine and/or serum pregnancy test will be required within 7 days prior to dosing on Day 1 of each cycle (local laboratory). Monthly pregnancy tests should be performed for WOCBP until the end of the study at the local laboratory. The serum pregnancy test should not be older than 72 hours before taking the first dose and can be done locally. The subsequent monthly serum pregnancy tests should be done at Day 1 of each Cycle for the first 6 cycles until Cycle 13. Of note to sites, if the urine test is the choice and is positive or cannot be confirmed as negative, a serum pregnancy test must be completed to confirm pregnancy result.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor/designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor/designee. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor/designee within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The

Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor.

- The Investigator must follow the pregnancy either to term or termination and will collect data on both maternal and fetal outcomes until final outcome (ie, normal, abnormal including abortion). Pregnancy alone is not considered an AE.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor/designee as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

Appendix 8 Genetics

Use/Analysis of DNA

- Genetic variation may impact a subject's response to study treatment, susceptibility to, and severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting subjects.
- DNA samples will be used for genetic mutation profiling.
- The results of genetic mutation profiling may be reported in the clinical study report.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be discarded once this study is completed.

Appendix 9 Primary Myelofibrosis Definition

2016 WHO Diagnostic Criteria for PMF

	Primary myelofibrosis (PMF)[a]	
	Prefibrotic/early PMF (pre-PMF)	**Overt PMF**
Major criteria		
1	Megakaryocytic proliferation and atypia[b], without reticulin fibrosis >grade 1[c], accompanied by increased age-adjusted BM cellularity, granulocytic proliferation and often decreased erythropoiesis	Megakaryocyte proliferation and atypia[b] accompanied by either reticulin and/or collagen fibrosis (Grade 2 or 3)
2	Not meeting WHO criteria for *BCR-ABL1* + CML, PV, ET, MDS, or other myeloid neoplasm	Not meeting WHO criteria for *BCR-ABL1* + CML, PV, ET, MDS or other myeloid neoplasm
3	Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker[d] or absence of minor reactive BM reticulin fibrosis[e]	Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence, the presence of another clonal marker[d] or absence of evidence for reactive BM fibrosis[f]
Minor criteria		
1	Presence of one or more of the following, confirmed in two consecutive determinations: • Anemia not attributed to a comorbid condition • Leukocytosis ≥11 × 10^9/L • Palpable splenomegaly • Serum LDH level above the upper limit of the institutional reference range	Presence of one or more of the following confirmed in two consecutive determinations: • Anemia not attributed to a comorbid condition • Leukocytosis ≥11 × 10^9/L • Palpable splenomegaly • Serum LDH level above the upper limit of the institutional reference range • Leukoerythroblastosis

Abbreviations: BM=bone marrow; CML=chronic myeloid leukemia; LDH= lactate dehydrogenase; MDS=myelodysplastic syndrome; PMF = primary myelofibrosis; WHO=World Health Organization.

[a] Diagnosis of prefibrotic/early PMF requires all three major criteria and at least one minor criterion. Diagnosis of overt PMF requires meeting all three major criteria and at least one minor criterion.

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

[c] In cases with Grade 1 reticulin fibrosis, the megakaryocyte changes must be accompanied by increased BM cellularity, granulocytic proliferation, and often decreased erythropoiesis (that is, pre-PMF).

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

[e] Minor (Grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

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

Source: Barbui T. Thiele J. Gisslinger H, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. Blood Cancer Journal. 2018;8:15; Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasm and acute leukemia. Blood. 2016;127(20):2391-405.

Appendix 10 Post-Polychythemia Vera Myelofibrosis Definition

2008 IWG-MRT Diagnostic Criteria for post-polycythemia vera myelofibrosis

Required criteria:

1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale)[a]

Additional criteria (two are required):

1. Anemia[b] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Abbreviations: IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; WHO=World Health Organization.

[a] Grade 2–3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

[b] Below the reference range for appropriate age, sex, gender and altitude considerations.

Source: Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of pos-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia. 2008;22:437-438.

Appendix 11 Post-Essential Thrombocythemia Myelofibrosis Definition

2008 IWG-MRT Diagnostic Criteria for post-essential thrombocythemia myelofibrosis

Required criteria:

1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria
2. Bone marrow fibrosis Grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale)[a]

Additional criteria (two are required):

1. Anemia[b] and a ≥2 mg/mL decrease from baseline hemoglobin level
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Increased LDH (above reference level)
5. Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Abbreviations: IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; LDH=lactate dehydrogenase; WHO=World Health Organization.

[a] Grade 2–3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

[b] Below the reference range for appropriate age, sex, gender, and altitude considerations.

Source: Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of pos-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia. 2008;22:437-438.

Appendix 12 Dynamic International Prognostic Scoring System

The DIPSS includes the same 5 prognostic factors as the IPSS but ascribes greater weight to low hemoglobin (2 points instead of 1) while the other risk factors are counted as 1; risk scoring is modified accordingly, and corresponding median survival estimates for low-, intermediate 1-, intermediate 2-, and high-risk diseases range from not reached to 1.5 years.

DIPSS Risk and Survival		
Risk category	**Number of risk factors**	**Median survival (years)**
Low	0	Not reached
Intermediate-1	1-2	14.2
Intermediate-2	3-4	4
High	5-6	1.5

The 5 adverse prognostic factors identified as predictors of shortened survival are:

- Age >65 years
- Constitutional symptoms
- Hemoglobin <10 g/dL
- White blood cell count >25 × 10^9/L
- Peripheral blood blasts ≥1%

Subjects are assigned into one of 4 risk categories based on the number of risk factors present.

DIPSS for Survival in Primary Myelofibrosis			
	Value		
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	N	Y	

The risk category is obtained adding up the values of each prognostic variable. Risk categories are defined as low: 0; intermediate-1: 1 or 2; intermediate-2: 3 or 4; and high: 5 or 6.

Source: Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010;115(9):1703-8.

Appendix 13 Eastern Cooperative Oncology Group (ECOG) Performance Status

These scales and criteria are used by doctors and researchers to assess how a subject's disease is progressing, assess how the disease affects the daily living abilities of the subject, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

Grade	ECOG Performance Status*
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, eg, light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed and chair.
5	Dead

* As published in: Oken MM, Creech RH, Tormey DC, et al. Am J Clin Oncol. 1982;5(6):649-55.
Source: npcrc.org/files/new/ECOG_performance_status.pdf.

Appendix 14 Revised Response Criteria for Myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) Consensus Report

Response categories	**Required criteria (for all response categories, benefit must last for ≥12 weeks to qualify as a response)**
Complete response (CR)	Bone marrow:[*] Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF[†] AND Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells[‡] AND Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Partial response (PR)	Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells[‡] AND Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH **OR** Bone marrow:[*] Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF[†] AND Peripheral blood: Hemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥50, but <100 × 10^9/L and <UNL; <2% immature myeloid cells[‡] AND Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia[§]
Anemia response	Transfusion-independent subjects: a ≥20 g/L increase in hemoglobin level[‖] Transfusion-dependent subjects: becoming transfusion-independent[{]
Spleen response[#]	A baseline splenomegaly that is palpable at 5 to 10 cm, below the LCM, becomes not palpable[**] **OR** A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%[**] A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response. A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction.
Symptoms response	A ≥50% reduction in the MPN-SAF TSS[††]
Progressive disease[‡‡]	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM **OR** A ≥100% increase in palpable disease, below LCM, for baseline splenomegaly of 5 to 10 cm **OR** A 50% increase in palpable distance, below LCM, for baseline splenomegaly of 10 cm **OR**

Response categories	**Required criteria (for all response categories, benefit must last for ≥12 weeks to qualify as a response)**
	Leukemic transformation confirmed by a bone marrow blast count of ≥20% **OR** 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
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI **OR** Loss of anemia response persisting for at least 1 month **OR** Loss of spleen response persisting for at least 1 month
Recommendations for assessing treatment-induced cytogenic and molecular changes	
Cytogenetic remission	At least 10 metaphases must be analyzed for cytogenetic response evaluation and requires confirmation by repeat testing within 6 months window. CR: eradication of a pre-existing abnormality PR: ≥50% reduction in abnormal metaphases (partial response applies only to subjects with at least 10 abnormal metaphases at baseline)
Molecular remission	Molecular response evaluation must be analyzed in peripheral blood granulocytes and requires confirmation by repeat testing within 6 months window. CR: Eradication of a pre-existing abnormality PR: ≥50% decrease in allele burden (partial response applies only to subjects with at least 20% mutant allele burden at baseline)
Cytogenetic/molecular relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

Abbreviations: EMH=extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH); LCM=left costal margin; MF=myelofibrosis; UNL=upper normal limit.

* Baseline and post-treatment bone marrow slides are to be interpreted locally at one sitting preferably by the same assessor. Cytogenetic and molecular responses are not required for CR assignment.

† Grading of MF is according to the European classification (Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005;90:1128). It is underscored that the consensus definition of a CR bone marrow is to be used only in those subjects in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

‡ Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized subjects, 5% immature myeloid cells is allowed.

§ See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the CTCAE version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25,000 × 10^9/L and absolute neutrophil count of ≥0.5 × 10^9/L.

‖ Applicable only to subjects with baseline hemoglobin of <100 g/L. In subjects not meeting the strict criteria for transfusion dependency at the time of study enrolment (see as follows), but have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.

{ 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, for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent subjects requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L.

In splenectomized subjects, palpable hepatomegaly is substituted with the same measurement strategy.

** Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

†† Symptoms are evaluated by the MPN-SAF TSS. The MPN-SAF TSS is assessed by the subjects themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

‡‡ Progressive disease assignment for splenomegaly requires confirmation by MRI or computed tomography showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to post-treatment measurements.

Source: Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood 2013;122:1395-1398.

Appendix 15 Schedule of Assessments for South Korea Only

Visit Timing	Screening	Cycle 1				Cycle 2		Cycle 3		Cycle 4	
	Day −28 to Day 0	Day 1 (Day 1/ WK 0)	Day 8 (Day 8/Wk 1)	Day 15 (Day 15/ WK 2)	Day 22 (Day 8/Wk 3)	Day 1 (Day 29/ WK 4)	Day 15 (Day 43/ WK 6)	Day 1 (Day 57/ WK 8)	Day 15 (Day 71/ WK 10)	Day 1 (Day 85/ WK 12)	Day 15 (Day 99/ WK 14)
Visit Window			+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days
Study Procedure											
Informed consent	X										
Review/confirm eligibility criteria	X	X									
COVID-19 status verification	X										
Genetic substudy informed consent (optional)	X										
Medical history	X[a]										
Physical examination	X[b]					X[c]		X[c]		X[c]	
Inactive (latent) TB test (local laboratory)	X										
MRI/CT (spleen volume measurement)	X[d]									X	
Vital signs	X	X				X		X		X	
ECOG PS	X	X[e]									
Clinical laboratory[f]	X	X[e]	X	X	X	X	X	X	X	X	X
Active tuberculosis (local lab)	X										

Visit Timing	Screening	Cycle 1				Cycle 2		Cycle 3		Cycle 4	
	Day −28 to Day 0	Day 1 (Day 1/ WK 0)	Day 8 (Day 8/Wk 1)	Day 15 (Day 15/ WK 2)	Day 22 (Day 8/Wk 3)	Day 1 (Day 29/ WK 4)	Day 15 (Day 43/ WK 6)	Day 1 (Day 57/ WK 8)	Day 15 (Day 71/ WK 10)	Day 1 (Day 85/ WK 12)	Day 15 (Day 99/ WK 14)
Visit Window			+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days
Pregnancy test (serum)	X										
12-lead ECG	X[g]	X[g]		X[g]		X[g]				X[g]	
PK sampling (NS-018 treatment arm only)		X				X					
Bone marrow assessment	X[h]										
Response assessment (IWG-MRT and ELN)						X		X		X	
Genetic profiling		X[e]									
Phospho-STAT3 (NS-018 treatment arm only)		X[e]				X					
mRNA sequencing (NS-018 treatment arm only)		X[e]				X					
MF-SAF v4.0[i]	←										→
PROMIS[j]	←										→
EQ-5D-5L		X[e]									
Randomization		X[m]									
Dispense study treatment/diary		X[e]				X		X		X	

Visit Timing	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4**	
	Day −28 to Day 0	**Day 1 (Day 1/ WK 0)**	**Day 8 (Day 8/Wk 1)**	**Day 15 (Day 15/ WK 2)**	**Day 22 (Day 8/Wk 3)**	**Day 1 (Day 29/ WK 4)**	**Day 15 (Day 43/ WK 6)**	**Day 1 (Day 57/ WK 8)**	**Day 15 (Day 71/ WK 10)**	**Day 1 (Day 85/ WK 12)**	**Day 15 (Day 99/ WK 14)**
Visit Window			**+3 days**	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**+3 days**
Administer study treatment (NS-018)		←									
Administer study treatment (BAT)[n]		←									
AEs	X	X[e]		X		X	X	X	X	X	X
Concomitant therapies/procedures/medication	X	X[e]		X		X	X	X	X	X	X

Visit Timing	**Cycle 5**		**Cycle 6**		**Cycle ≥7**	**Complete End-of-Study Procedures[l, o]**	**End of Study**
	Day 1 (Day 113/ WK16)	**Day 15 (Day 127/ WK18)**	**Day 1 (Day 141/ WK20)**	**Day 15 (Day 155/ WK22)**	**Day 1 (Every +Day28/WK4)**		**30-Day Follow-up (Phone call)[p]**
Visit Window	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**±1 week**		**±3 days**
Physical examination					X[c] (Every 3 cycles)	X[b]	

Visit Timing	**Cycle 5**		**Cycle 6**		**Cycle ≥7**	**Complete End-of-Study Procedures[l, o]**	**End of Study**
	Day 1 (Day 113/ WK16)	**Day 15 (Day 127/ WK18)**	**Day 1 (Day 141/ WK20)**	**Day 15 (Day 155/ WK22)**	**Day 1 (Every +Day28/WK4)**		**30-Day Follow-up (Phone call)[p]**
Visit Window	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**±1 week**		**±3 days**
MRI/CT (spleen volume measurement)					X (Cycles 7, 10, 13)	X[k]	
Vital signs	X		X		X	X	
ECOG PS						X	
Clinical laboratory[f]	X	X	X	X	X	X	
Pregnancy test (serum)						X	
12-lead ECG[g]					X (Every 3 cycles)	X	
Bone marrow assessment					X (Cycles 13; every 12 cycles thereafter)		
Response assessment (IWG-MRT and ELN)					X (Every 3 cycles)	X	
MF-SAF v4.0[i]	←	—	—	—	→ (Up to Cycle 12)		
PROMIS[j]	←	—	—	—	→ (Up to Cycle 12)		

Visit Timing	Cycle 5		Cycle 6		Cycle ≥7	Complete End-of-Study Procedures[l, o]	End of Study
	Day 1 (Day 113/ WK16)	Day 15 (Day 127/ WK18)	Day 1 (Day 141/ WK20)	Day 15 (Day 155/ WK22)	Day 1 (Every +Day28/WK4)		30-Day Follow-up (Phone call)[p]
Visit Window	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**±1 week**		**±3 days**
EQ-5D-5L					X (Every 6 cycles)		
Dispense study treatment/diary	X		X		X (Every 3 cycles)		
Administer study treatment (NS-018)	→	→	→	→	→		
Administer study treatment (BAT)[n]	→	→	→	→	(Transition to NS-018)		
AE	X	X	X	X	X	X	X
Concomitant therapies/procedures/ medication	X	X	X	X	X	X	X

Abbreviations: AEs=adverse events; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BAT=Best Available Therapy; BUN=blood urea nitrogen; COVID-19=coronavirus disease 2019; eCRF=electronic case report form; EQ-5D-5L = 5-level EQ-5D version; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; ELN=European LeukemiaNet; IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; LDH=lactate dehydrogenase; mRNA=messenger ribonucleic acid; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; MF-SAF v4.0=Myelofibrosis Symptom Assessment Form version 4.0; MRI=magnetic resonance imaging; PK=pharmacokinetics; PROMIS=Patient-Reported Outcomes Measurement Information System; QD=once daily; STAT3=signal transducer and activator of transcription 3; WK=week.

NOTE: At Cycle 1 Day 1, before the subject starts study treatment, all eligibility criteria including the subject's COVID-19 status should be reviewed and confirmed.

NOTE: Verification of COVID-19 status is based on the World Health Organization diagnostic criteria (Public health surveillance for COVID-19. Interim guidance; 07 August 2020). If a subject presents with clinical signs and symptoms consistent with COVID-19 infection, the Investigator should request a test where possible and this should be recorded in the AE field of the eCRF.

[a] Including concomitant medications within 28 days prior to study treatment administration, blood products transfused within 3 months prior to study treatment administration, and concurrent baseline conditions.

[b] Full physical examination including weight and spleen size by clinical assessment (palpation). At screening, spleen size (palpation) measurement should be done on the same day the spleen volume is measured by MRI. If the same day measurement is not feasible, the measurement should be assessed within 14 days prior to the first dose of the study treatment.

[c] Directed physical examination including weight and spleen size by palpation.
[d] Assess spleen volume within 14 days prior to the first dose of the study treatment.
[e] Predose; may be obtained within 24 hours prior to study treatment administration. AEs on Cycle 1 Day 1 will also be collected postdose.
[f] Safety laboratory assessments will be performed on Cycle 1 Days 1, 8, 15, and 22, Cycle 2 through Cycle 6 on Days 1 and 15, and Day 1 of each cycle thereafter at minimum. For subjects who transition to NS-018, safety laboratory assessments will be performed on Day 1 and Day 15 of each cycle for the first 6 cycles after transitioning to NS-018 (including the additional visits on Day 8 and Day 22 of the first cycle after transitioning). Hematology includes erythrocytes, MCV, MCH, neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin, and hematocrit. Serum chemistry includes BUN, LDH, creatinine, uric acid, total protein, albumin, glucose, direct bilirubin for screening, total bilirubin (for safety assessment), magnesium, ALP, AST, ALT, chloride, sodium, potassium, amylase, and lipase. Urinalysis includes pH, protein, glucose, ketone, bilirubin, blood, and nitrite. Assessments on Day 8 and Day 22 of Cycle 1 for subjects randomized to NS-018 or Cycle 1 after transitioning to NS-018 in subjects who transition to NS-018 will be performed at the institutional local laboratory. All other safety laboratory assessments will be performed at the central laboratory. Additional local laboratory assessments may be performed per Investigator's discretion to monitor safety and document AEs as per local standards of care.
[g] For eligibility determination; median QTcF must be ≤480 msec. For screening, Cycles 1 and 2, triplicate central reading, and then from Cycle 4 onwards, single central reading. ECGs for Cycle 1 Day 1: Predose (3 time points within 1 hour) and 1, 2, 4, 6, 8 (±10 minutes) hours after administration of NS-018, Cycle 1 Day 15: 2 (±10 minutes) hours after administration of NS-018, Cycle 2 Day 1: Predose (within 1 hour) and 1, 2, 4 (±10 minutes) hours after administration of NS-018, and Cycle 4 Day 1 and thereafter every 3 cycles: 2 (±10 min) hours after administration of NS-018.
[h] Within 28 days prior to the first dose of study drug. However, bone marrow assessment performed within 6 months prior to the first dose can be used as baseline.
[i] During the screening period, subjects will complete the MF-SAF v4.0 assessment daily. The first 7 consecutive days of diary data will be used for eligibility assessments. Subjects will complete the MF-SAF daily from Day −7 of Cycle 1 Day 1 to the end of Cycle 6 (Day 168) and the last 7 days in each cycle thereafter until the end of Cycle 12 (Day 336) for efficacy assessment.
[j] The PROMIS questionnaire must be completed daily during the screening period and the last 7 days of each cycle until the end of Cycle 12 (Day 336). This assessment will be performed for all subjects including subjects transitioning from BAT to NS-018.
[k] If not done within the previous 8 weeks.
[l] Within 14 days after last dose of study treatment or within 14 days after withdrawal from the study.
[m] Randomization can be done within Day −4 so that the subject can start study treatment on the morning of Day 1.
[n] In the BAT treatment arm (control group), after subjects have completed treatment with BAT at the end of Cycle 6, subjects will discontinue BAT and transition to NS-018 at Cycle 7 Day 1. During this transition period, subjects treated with ruxolitinib will be required to taper off this treatment before initiation of NS-018. The dose of ruxolitinib should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration for the total tapering period of 14 days. Ruxolitinib should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of ruxolitinib are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of ruxolitinib therapy) is noted, it is strongly suggested that therapy with ruxolitinib be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended. Subjects administered with treatment other than ruxolitinib will undergo a minimum washout period of 1 week (7 days) prior to start of NS-018 treatment.
[o] Subjects who discontinue study treatment or withdraw from the study will be asked to complete the end of study procedures within 14 days after the last dose. If the end of study procedures occur at a regular scheduled visit, these procedures may be performed at that time.
[P] Follow-up phone call will be done 30 (±3) days after the completion of end of study procedures.

Additional Assessment Guidance

The table below clarifies the timing of specific assessment completion.

Assessments	Time restriction	
	Predose	**Postdose**
Pharmacokinetics (NS-018 treatment arm only)	Within 1 hour	**Cycle 1 Day 1** 0.5, 1, 2, 3, 4, 6, 8 hours (±10 min per time point) **Cycle 2 Day 1** 0.5, 1, 2, 3, 4, 6, 8 hours (±10 min per time point)
Vital signs	Within 3 hours	Not applicable
ECOG performance status	Within 24 hours	Not applicable
12-lead ECG (NS-018 treatment arm only)	**Cycle 1 Day 1** 3 time points within 1 hour (eg, -45, -30, -15 min) **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 5 time points: 1, 2, 4, 6, and 8 hours (±10 min per time point) **Cycle 1 Day 15** 2 (±10 min) hours **Cycle 2 Day 1** 3 time points: 1, 2, and 4 hours (±10 min per time point) **Cycle 4 Day 1 and thereafter every 3 cycles** 2 (±10 min) hours
Phospho-STAT3 (NS-018 treatment arm only)	**Cycle 1 Day 1** Within 24 hours **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 3 hours (±10 min) **Cycle 2 Day 1** 3 hours (±10 min)
mRNA sequencing (NS-018 treatment arm only)	**Cycle 1 Day 1** Within 24 hours **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 8 hours (±10 min)

Abbreviations: ECG=electrocardiogram; ECOG= Eastern Cooperative Oncology Group; min=minutes; mRNA=messenger ribonucleic acid sequencing; STAT3=signal transducer and activator of transcription 3.

Appendix 16 Schedule of Assessments for UK only

Visit Timing	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	Day −28 to Day 0	Day 1 (Day 1/ WK 0)	Day 15 (Day 15/ WK 2)	Day 1 (Day 29/ WK 4)	Day 15 (Day 43/ WK 6)	Day 1 (Day 57/ WK 8)	Day 15 (Day 71/ WK 10)	Day 1 (Day 85/ WK 12)	Day 15 (Day 99/ WK 14)
Visit Window			+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days
Study Procedure									
Informed consent	X								
Review/confirm eligibility criteria	X	X							
COVID-19 status verification	X								
Genetic substudy informed consent (optional)	X								
Medical history	X[a]								
Physical examination	X[b]			X[c]		X[c]		X[c]	
Inactive (latent) TB test (local laboratory)	X								
MRI/CT (spleen volume measurement)	X[d]							X	
Vital signs	X	X		X		X		X	
ECOG PS	X	X[e]							
Clinical laboratory[f] (by central lab)	X	X[e]	X	X	X	X	X	X	X
Pregnancy test (serum)[q]	X			X		X		X	
12-lead ECG	X[g]	X[g]	X[g]	X[g]		X[g]		X[g]	
PK sampling (NS-018 treatment arm only)		X		X					
Bone marrow assessment	X[h]								

Visit Timing	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	Day −28 to Day 0	Day 1 (Day 1/ WK 0)	Day 15 (Day 15/ WK 2)	Day 1 (Day 29/ WK 4)	Day 15 (Day 43/ WK 6)	Day 1 (Day 57/ WK 8)	Day 15 (Day 71/ WK 10)	Day 1 (Day 85/ WK 12)	Day 15 (Day 99/ WK 14)
Visit Window			+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days
Study Procedure									
Response assessment (IWG-MRT and ELN)				X		X		X	
Genetic profiling		X[e]							
Phospho-STAT3 (NS-018 treatment arm only)		X[e]		X					
mRNA sequencing (NS-018 treatment arm only)		X[e]		X					
MF-SAF v4.0[i]	←	←	←	←	←	←	←	←	←
PROMIS[j]	←	←	←	←	←	←	←	←	←
EQ-5D-5L		X[e]							
Randomization		X[m]							
Dispense study treatment/diary		X[e]		X		X		X	
Administer study treatment (NS-018)		←	←	←	←	←	←	←	←
Administer study treatment (BAT)[n]		←	←	←	←	←	←	←	←
AEs	X	X[e]	X	X	X	X	X	X	X
Concomitant therapies/procedures/medication	X	X[e]	X	X	X	X	X	X	X

Visit Timing	Cycle 5		Cycle 6		Cycle ≥7	Complete End-of-Study Procedures[l, o]	End of Study
	Day 1 (Day 113/ WK16)	Day 15 (Day 127/ WK18)	Day 1 (Day 141/ WK20)	Day 15 (Day 155/ WK22)	Day 1 (Every +Day28/WK4)		30-Day Follow-up (Phone call)[p]
Visit Window	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**±1 week**		**±3 days**
Study Procedure							
Physical examination					X[c] (Every 3 cycles)	X[b]	
MRI/CT (spleen volume measurement)					X (Cycles 7, 10, 13)	X[k]	
Vital signs	X		X		X	X	
ECOG PS						X	
Clinical laboratory[f] (by central lab)	X	X	X	X	X	X	
Pregnancy test (serum)[q]	X		X		X	X	
12-lead ECG					X (Every 3 cycles)[g]	X	
PK sampling (NS-018 treatment arm only)							
Bone marrow assessment					X (Cycles 13; every 12 cycles thereafter)		
Response assessment (IWG-MRT and ELN)					X (Every 3 cycles)	X	
Genetic profiling							
MF-SAF v4.0[i]	→	→	→	→	→ (Up to Cycle 12)		

Visit Timing	Cycle 5		Cycle 6		Cycle ≥7	Complete End-of-Study Procedures[l, o]	End of Study
	Day 1 (Day 113/ WK16)	Day 15 (Day 127/ WK18)	Day 1 (Day 141/ WK20)	Day 15 (Day 155/ WK22)	Day 1 (Every +Day28/WK4)		30-Day Follow-up (Phone call)[p]
Visit Window	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**±1 week**		**±3 days**
Study Procedure							
PROMIS[j]	→	→	→	→	→ (Up to Cycle 12)		
EQ-5D-5L					X (Every 6 cycles)		
Dispense study treatment/diary	X		X		X (Every 3 cycles)		
Administer study treatment (NS-018)	→	→	→	→	→		
Administer study treatment (BAT)[n]	→	→	→	→	(Transition to NS-018)		
AE	X	X	X	X	X	X	X
Concomitant therapies/procedures/ medication	X	X	X	X	X	X	X

Abbreviations: AEs=adverse events; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BAT=Best Available Therapy; BUN=blood urea nitrogen; COVID-19=coronavirus disease 2019; eCRF=electronic case report form; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; ELN=European LeukemiaNet; EQ-5D-5L=5-level EQ-5D version;IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; LDH=lactate dehydrogenase; MF=myelofibrosis; mRNA=messenger ribonucleic acid; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; MF-SAF v4.0=Myelofibrosis Symptom Assessment Form version 4.0; MRI=magnetic resonance imaging; PK=pharmacokinetics; PROMIS=Patient-Reported Outcomes Measurement Information System; QD=once daily; STAT3=signal transducer and activator of transcription 3; TB=tuberculosis; WOCBP=women of childbearing potential; WK=week.

NOTE: At Cycle 1 Day 1, before the subject starts study treatment, all eligibility criteria including the subject's COVID-19 status should be reviewed and confirmed.

NOTE: Verification of COVID-19 status is based on the World Health Organization diagnostic criteria (Public health surveillance for COVID-19. Interim guidance, 07 August 2020). If a subject presents with clinical signs and symptoms consistent with COVID-19 infection, the Investigator should request a test where possible and this should be recorded in the AE field of the eCRF.

[a] Including concomitant medications within 28 days prior to study treatment administration, blood products transfused within 3 months prior to study treatment administration, and concurrent baseline conditions.

[b] Full physical examination including weight and spleen size by clinical assessment (palpation). At screening, spleen size (palpation) measurement must be done on the same day the spleen volume is measured by MRI.

[c] Directed physical examination including weight and spleen size by palpation. A skin examination will also be conducted as part of the physical examination.

[d] Assess spleen volume within 14 days prior to the first dose of the study treatment.

[e] Predose; may be obtained within 24 hours prior to study treatment administration. AEs on Cycle 1 Day 1 will also be collected postdose.

[f] Subjects transitioning from BAT to NS-018 before or at Cycle 7 Day 1 will have safety laboratory assessments performed on Day 1 and 15 of each cycle for 6 cycles. Safety laboratory assessments will continue on Day 1 of the following cycles until the end of the study. Hematology includes erythrocytes, MCV, MCH, neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin, and hematocrit. Serum chemistry includes BUN, LDH, creatinine, uric acid, total protein, albumin, glucose, direct bilirubin (for screening) total bilirubin (safety assessment), magnesium, ALP, AST, ALT, chloride, sodium, potassium, amylase, and lipase. Urinalysis includes pH, protein, glucose, ketone, bilirubin, blood, and nitrite. Note: Additional local laboratory assessments may be performed per Investigator's discretion to monitor safety and document AEs as per local standards of care.

[g] For eligibility determination; median QTcF must be ≤480 msec. For screening, Cycles 1 and 2, triplicate central reading, and then from Cycle 4 onwards, single central reading. ECGs Cycle 1 Day 1: Predose (3 time points within 1 hour) and 1, 2, 4, 6, 8 (±10 minutes) hours after administration of NS-018, Cycle 1 Day 15: 2 (±10 minutes) hours after administration of NS-018, Cycle 2 Day 1: Predose (within 1 hour) and 1, 2, 4 (±10 minutes) hours after administration of NS-018, Cycle 3 Day 1 predose (within 1 hour) and 1, 2, and 4 (±10 minutes) hours after administration of NS-018, and Cycle 4 Day 1 and thereafter every 3 cycles: 2 (±10 minutes) hours after administration of NS-018. NOTE: An additional single ECG will be done at Cycle 3 and Cycle 9, Day 1 predose (within 1 hour) and 1, 2, and 4 (±10 minutes) hours after administration of NS-018.

[h] Within 28 days prior to the first dose of study drug. However, bone marrow assessment performed within 6 months prior to the first dose can be used as baseline.

[i] During the screening period, subjects will complete the MF-SAF v4.0 assessment daily. The first 7 consecutive days of diary data will be used for eligibility assessments. Subjects will complete the MF-SAF daily from Day −7 of Cycle 1 Day 1 to the end of Cycle 6 (Day 168) and the last 7 days in each cycle thereafter until the end of Cycle 12 (Day 336) for efficacy assessment.

[j] The PROMIS questionnaire must be completed daily during the screening period and the last 7 days of each cycle until the end of Cycle 12 (Day 336). This assessment will be performed for all subjects including subjects transitioning from BAT to NS-018.

[k] If not done within the previous 8 weeks.

[l] Within 14 days after last dose of study treatment or within 14 days after withdrawal from the study.

[m] Randomization can be done within Day −4 so that the subject can start study treatment on the morning of Day 1.

[n] In the BAT treatment arm (control group), after subjects have completed treatment with BAT at the end of Cycle 6, subjects will discontinue BAT and transition to NS-018 at Cycle 7 Day 1. During this transition period, subjects treated with ruxolitinib will be required to taper off this treatment before initiation of NS-018. The dose of ruxolitinib should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration for the total tapering period of 14 days. Ruxolitinib should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of ruxolitinib are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of ruxolitinib therapy) is noted, it is strongly suggested that therapy with ruxolitinib be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended. Subjects administered with treatment other than ruxolitinib will undergo a minimum washout period of 1 week (7 days) prior to start of NS-018 treatment.

[o] Subjects who discontinue study treatment or withdraw from the study will be asked to complete the end of study procedures within 14 days after the last dose. If the end of study procedures occur at a regular scheduled visit, these procedures may be performed at that time.

[p] Follow-up phone call will be done 30 (±3) days after the completion of end of study procedures.

[q] For WOCBP only, a negative serum pregnancy test will be required within 7 days prior to dosing on Cycle 1 Day 1, and a negative urine and/or serum pregnancy test will be required within 7 days prior to dosing on Day 1 of each cycle (local laboratory). Of note to sites, if the urine test is the choice and is positive or cannot be confirmed as negative, a serum pregnancy test must be completed to confirm pregnancy result.
WOCBP will have pregnancy tests done monthly for early detection of pregnancy and discontinuation of study drugs.

Additional Assessment Guidance

The table below clarifies the timing of specific assessment completion.

Assessments	Time restriction	
	Predose	**Postdose**
Pharmacokinetics (NS-018 treatment arm only)	Within 1 hour	**Cycle 1 Day 1** 0.5, 1, 2, 3, 4, 6, 8 hours (±10 min per time point) **Cycle 2 Day 1** 0.5, 1, 2, 3, 4, 6, 8 hours (±10 min per time point)
Vital signs	Within 3 hours	Not applicable
ECOG performance status	Within 24 hours	Not applicable
12-lead ECG	**Cycle 1 Day 1** 3 time points within 1 hour (eg, -45, -30, -15 min) **Cycle 2 Day 1** Within 1 hour **Cycle 3 Day 1 (for UK only)** Within 1 hour	**Cycle 1 Day 1** 5 time points: 1, 2, 4, 6, and 8 hours (±10 min per time point) **Cycle 1 Day 15** 2 (±10 min) hours **Cycle 2 Day 1** 3 time points: 1, 2, and 4 hours (±10 min per time point) **Cycle 3 Day 1** 3 time points: 1, 2, and 4 hours (±10 min per time point) **Cycle 4 Day 1 and thereafter every 3 cycles** 2 (±10 min) hours
Phospho-STAT3 (NS-018 treatment arm only)	**Cycle 1 Day 1** Within 24 hours **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 3 hours (±10 min) **Cycle 2 Day 1** 3 hours (±10 min)
mRNA sequencing (NS-018 treatment arm only)	**Cycle 1 Day 1** Within 24 hours **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 8 hours (±10 min)

Abbreviations: ECG=electrocardiogram; ECOG= Eastern Cooperative Oncology Group; min=minutes; mRNA=messenger ribonucleic acid sequencing; STAT3=signal transducer and activator of transcription 3.

Appendix 17 Schedule of Assessments for Germany Only

Visit Timing	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	Day −28 to Day 0	Day 1 (Day 1/ WK 0)	Day 15 (Day 15/ WK 2)	Day 1 (Day 29/ WK 4)	Day 15 (Day 43/ WK 6)	Day 1 (Day 57/ WK 8)	Day 15 (Day 71/ WK 10)	Day 1 (Day 85/ WK 12)	Day 15 (Day 99/ WK 14)
Visit Window			+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days
Study Procedure									
Informed consent	X								
Review/confirm eligibility criteria	X	X							
COVID-19 status verification	X								
Genetic substudy informed consent (optional)	X								
Medical history	X[a]								
Physical examination	X[b]			X[c]		X[c]		X[c]	
MRI/CT (spleen volume measurement)	X[d]							X	
Vital signs	X	X		X		X		X	
ECOG PS	X	X[e]							
Active tuberculosis	X								
Clinical laboratory[f] (by central lab)	X	X[e]	X	X	X	X	X	X	X
Pregnancy test (serum) (local laboratory)	X	X		X		X		X	

Visit Timing	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	Day −28 to Day 0	Day 1 (Day 1/ WK 0)	Day 15 (Day 15/ WK 2)	Day 1 (Day 29/ WK 4)	Day 15 (Day 43/ WK 6)	Day 1 (Day 57/ WK 8)	Day 15 (Day 71/ WK 10)	Day 1 (Day 85/ WK 12)	Day 15 (Day 99/ WK 14)
Visit Window			+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days
12-lead ECG	X[g]	X[g]	X[g]	X[g]				X[g]	
PK sampling (NS-018 treatment arm only)		X		X					
Bone marrow assessment	X[h]								
Response assessment (IWG-MRT and ELN)				X		X		X	
Genetic profiling		X[e]							
Phospho-STAT3 (NS-018 treatment arm only)		X[e]		X					
mRNA sequencing (NS-018 treatment arm only)		X[e]		X					
MF-SAF v4.0[i]	←								→
PROMIS[j]		←							→
EQ-5D-5L		X[e]							
Randomization		X[m]							
Dispense study treatment/diary		X[e]		X		X		X	
Administer study treatment (NS-018)		←							→
Administer study treatment (BAT)[n]		←							→

Visit Timing	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	Day −28 to Day 0	Day 1 (Day 1/ WK 0)	Day 15 (Day 15/ WK 2)	Day 1 (Day 29/ WK 4)	Day 15 (Day 43/ WK 6)	Day 1 (Day 57/ WK 8)	Day 15 (Day 71/ WK 10)	Day 1 (Day 85/ WK 12)	Day 15 (Day 99/ WK 14)
Visit Window			+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days
AEs	X	X[e]	X	X	X	X	X	X	X
Concomitant therapies/procedures/medication	X	X[e]	X	X	X	X	X	X	X

Visit Timing	Cycle 5		Cycle 6		Cycle ≥7	Complete End-of-Study Procedures[l, o]	End of Study
	Day 1 (Day 113/ WK16)	Day 15 (Day 127/ WK18)	Day 1 (Day 141/ WK20)	Day 15 (Day 155/ WK22)	Day 1 (Every +Day28/WK4)		30-Day Follow-up (Phone call)[p]
Visit Window	+3 days	+3 days	+3 days	+3 days	±1 week		±3 days
Study procedure							
Physical examination					X[c] (Every 3 cycles)	X[b]	
MRI/CT (spleen volume measurement)					X (Cycles 7, 10, 13)	X[k]	
Vital signs	X		X		X	X	
ECOG PS						X	
Clinical laboratory[f] (by central lab)	X	X	X	X	X	X	

Visit Timing	**Cycle 5**		**Cycle 6**		**Cycle ≥7**	**Complete End-of-Study Procedures[l, o]**	**End of Study**
	Day 1 (Day 113/ WK16)	**Day 15 (Day 127/ WK18)**	**Day 1 (Day 141/ WK20)**	**Day 15 (Day 155/ WK22)**	**Day 1 (Every +Day28/WK4)**		**30-Day Follow-up (Phone call)[p]**
Visit Window	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**±1 week**		**±3 days**
Pregnancy test (serum)[q]	X		X		X	X	
12-lead ECG					X (Every 3 cycles)[g]	X	
Bone marrow assessment					X (Cycles 13; every 12 cycles thereafter)		
Response assessment (IWG-MRT and ELN)					X (Every 3 cycles)	X	
MF-SAF v4.0[i]	→	→	→	→	→ (Up to Cycle 12)		
PROMIS[j]	→	→	→	→	→ (Up to Cycle 12)		
EQ-5D-5L					X (Every 6 cycles)		
Dispense study treatment/diary	X		X		X (Every 3 cycles)		
Administer study treatment (NS-018)	→	→	→	→	→		
Administer study treatment (BAT)[n]	→	→	→	→	(Transition to NS-018)		
AE	X	X	X	X	X	X	X

Visit Timing	Cycle 5		Cycle 6		Cycle ≥7	Complete End-of-Study Procedures[l, o]	End of Study
	Day 1 (Day 113/ WK16)	Day 15 (Day 127/ WK18)	Day 1 (Day 141/ WK20)	Day 15 (Day 155/ WK22)	Day 1 (Every +Day28/WK4)		30-Day Follow-up (Phone call)[p]
Visit Window	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**±1 week**		**±3 days**
Concomitant therapies/procedures/ medication	X	X	X	X	X	X	X

Abbreviations: AEs=adverse events; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BAT=Best Available Therapy; BUN=blood urea nitrogen; COVID-19=coronavirus disease 2019; eCRF=electronic case report form; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; ELN=European LeukemiaNet; EQ-5D-5L = 5-level EQ-5D version; IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; LDH=lactate dehydrogenase; mRNA=messenger ribonucleic acid; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; MF=myelofibrosis; MF-SAF v4.0=Myelofibrosis Symptom Assessment Form version 4.0; MRI=magnetic resonance imaging; PK=pharmacokinetics; STAT3=signal transducer and activator of transcription 3; PROMIS=Patient-Reported Outcomes Measurement Information System; QD=once daily; WK=week; WOCBP = women of childbearing potential.

NOTE: At Cycle 1 Day 1, before the subject starts study treatment, all eligibility criteria including the subject's COVID-19 status should be reviewed and confirmed.

NOTE: Verification of COVID-19 status is based on the World Health Organization diagnostic criteria (Public health surveillance for COVID-19. Interim guidance; 07 August 2020). If a subject presents with clinical signs and symptoms consistent with COVID-19 infection, the Investigator should request a test where possible and this should be recorded in the AE field of the eCRF.

NOTE: Monthly pregnancy tests should be performed for women of childbearing potential. The serum pregnancy test should not be older than 72 hours before taking the first dose and can be done locally. The subsequent monthly serum pregnancy tests should be done at Day 1 of each Cycle until the end of the study.

NOTE: Subjects transitioning from BAT to NS-018 must be monitored as closely as subjects who are initially randomized to NS-018 with physical examination, vital signs, safety laboratory assessments and 12-lead ECG, etc., for the first cycles after transition to the NS-018 following the SoA from Cycle 1 Day 1.

[a] Including concomitant medications within 28 days prior to study treatment administration, blood products transfused within 3 months prior to study treatment administration, and concurrent baseline conditions.

[b] Full physical examination including weight and spleen size by clinical assessment (palpation). At screening, spleen size (palpation) measurement must be done on the same day the spleen volume is measured by MRI. If the same day measurement is not feasible, the measurement should be assessed within 14 days prior to the first dose of the study treatment.

[c] Directed physical examination including weight and spleen size by palpation.

[d] Assess spleen volume within 14 days prior to the first dose of the study treatment.

[e] Predose; may be obtained within 24 hours prior to study treatment administration. AEs on Cycle 1 Day 1 will also be collected postdose.

[f] Subjects transitioning from BAT to NS-018 before or at Cycle 7 Day 1 will have safety laboratory assessments performed on Day 1 and 15 of each cycle for 6 cycles. Safety laboratory assessments will continue on Day 1 of the following cycles until the end of the study. Hematology includes erythrocytes, MCV, MCH, neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin, and hematocrit. Serum chemistry includes BUN, LDH, creatinine, uric acid, total protein, albumin, glucose, direct bilirubin for screening, total bilirubin (for safety measurement), magnesium, ALP, AST, ALT, chloride, sodium, potassium, amylase, and lipase. Urinalysis includes pH, protein, glucose, ketone, bilirubin, blood, and nitrite. Additional local laboratory assessments may be performed per Investigator's discretion to monitor safety and document AEs as per local standards of care.

[g] For eligibility determination; median QTcF must be ≤480 msec. For screening, Cycles 1 and 2, triplicate central reading, and then from Cycle 4 onwards, single central reading. ECGs for Cycle 1 Day 1: Predose (3 time points within 1 hour) and 1, 2, 4, 6, 8 (±10 minutes) hours after administration of NS-018, Cycle 1 Day 15: 2 (±10 minutes) hours after administration of NS-018, Cycle 2 Day 1: Predose (within 1 hour) and 1, 2, 4 (±10 minutes) hours after administration of NS-018, and Cycle 4 Day 1 and thereafter every 3 cycles: 2 (±10 min) hours after administration of NS-018.

[h] Within 28 days prior to the first dose of study drug. However, bone marrow assessment performed within 6 months prior to the first dose can be used as baseline.

[i] During the screening period, subjects will complete the MF-SAF v4.0 assessment daily. The first 7 consecutive days of diary data will be used for eligibility assessments. Subjects will complete the MF-SAF daily from Day −7 of Cycle 1 Day 1 to the end of Cycle 6 (Day 168) and the last 7 days in each cycle thereafter until the end of Cycle 12 (Day 336) for efficacy assessment.

[j] The PROMIS questionnaire must be completed daily during the screening period and the last 7 days of each cycle until the end of Cycle 12 (Day 336). This assessment will be performed for all subjects including subjects transitioning from BAT to NS-018.

[k] If not done within the previous 8 weeks.

[l] Within 14 days after last dose of study treatment or within 14 days after withdrawal from the study.

[m] Randomization can be done within Day −4 so that the subject can start study treatment on the morning of Day 1.

[n] In the BAT treatment arm (control group), after subjects have completed treatment with BAT at the end of Cycle 6, subjects will discontinue BAT and transition to NS-018 at Cycle 7 Day 1. During this transition period, subjects treated with ruxolitinib will be required to taper off this treatment before initiation of NS-018. The dose of ruxolitinib should be decreased every 7 days by up to 50% until the smallest dose possible has been given for a minimum duration for the total tapering period of 14 days. Ruxolitinib should then be stopped 1 day before starting NS-018. Subjects who are taking 5 mg QD of ruxolitinib are already on the lowest dose possible; therefore, tapering is not applicable in this case. If recurrence of MF-related symptoms (upon discontinuation of ruxolitinib therapy) is noted, it is strongly suggested that therapy with ruxolitinib be restarted. If restart is not possible, then prompt therapy with corticosteroids (eg, prednisone 60 mg QD) is recommended. Subjects administered with treatment other than ruxolitinib will undergo a minimum washout period of 1 week (7 days) prior to start of NS-018 treatment.

[o] Subjects who discontinue study treatment or withdraw from the study will be asked to complete the end of study procedures within 14 days after the last dose. If the end of study procedures occur at a regular scheduled visit, these procedures may be performed at that time.

[P] Follow-up phone call will be done 30 (±3) days after the completion of end of study procedures.

[q] For WOCBP only, a negative serum pregnancy test will be required within 7 days prior to dosing on Cycle 1 Day 1, and a negative urine and/or serum pregnancy test will be required within 7 days prior to dosing on Day 1 of each cycle (local lab). Of note to sites, if the urine test is the choice and is positive or cannot be confirmed as negative, a serum pregnancy test must be completed to confirm pregnancy result. WOCBP will have pregnancy tests done monthly for early detection of pregnancy and discontinuation of study drugs.

Additional Assessment Guidance

The table below clarifies the timing of specific assessment completion.

Assessments	Time restriction	
	Predose	**Postdose**
Pharmacokinetics (NS-018 treatment arm only)	Within 1 hour	**Cycle 1 Day 1** 0.5, 1, 2, 3, 4, 6, 8 hours (±10 min per time point) **Cycle 2 Day 1** 0.5, 1, 2, 3, 4, 6, 8 hours (±10 min per time point)
Vital signs	Within 3 hours	Not applicable
ECOG performance status	Within 24 hours	Not applicable
12-lead ECG	**Cycle 1 Day 1** 3 time points within 1 hour (eg, -45, -30, -15 min) **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 5 time points: 1, 2, 4, 6, and 8 hours (±10 min per time point) **Cycle 1 Day 15** 2 (±10 min) hours **Cycle 2 Day 1** 3 time points: 1, 2, and 4 hours (±10 min per time point) **Cycle 4 Day 1 and thereafter every 3 cycles** 2 (±10 min) hours
Phospho-STAT3 (NS-018 treatment arm only)	**Cycle 1 Day 1** Within 24 hours **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 3 hours (±10 min) **Cycle 2 Day 1** 3 hours (±10 min)

Assessments	Time restriction	
	Predose	**Postdose**
mRNA sequencing (NS-018 treatment arm only)	**Cycle 1 Day 1** Within 24 hours **Cycle 2 Day 1** Within 1 hour	**Cycle 1 Day 1** 8 hours (±10 min)

Abbreviations: ECG=electrocardiogram; ECOG= Eastern Cooperative Oncology Group; min=minutes; mRNA=messenger ribonucleic acid sequencing; STAT3=signal transducer and activator of transcription 3.

Appendix 18 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment version 3.0 is located directly before the table of contents.

Protocol Amendment Summary of Change Table

DOCUMENT HISTORY			
Document	**Date**	**Substantial**	**Region**
Version 2.0	15 September 2022	Yes	Poland, Turkey, North America, and Asia
Original Protocol	13 October 2021		Europe, North America, and Asia

Amendment Global Version 2.0 (15 September 2022)

This amendment for all sites participating in this study is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety or physical/mental integrity of subjects, the scientific value of the study, given the phase of this study, study population and expected menopausal status/use of contraception for the enrolled subjects.

Overall Rationale for the Amendment:

This amendment to the original protocol version 1.0 (dated 13 October 2021), was amended to consolidate the changes requested by the Food and Drug Administration (FDA South Korean Competent Authority). Additionally, the protocol language related to contraception per Clinical Trials Facilitation Group (CTFG) guidance has been aligned to harmonize with EU submissions.

Section # and Name	**Description of Change**	**Brief Rationale**
Throughout	Updated version from original to Version 2.0, updated abbreviations and formatting as needed.	Changes required amendment and new version and updates to text, tables, formatting.
Sponsor Signatory page	Removed statement regarding medical monitor.	Removed names and contacts from Appendix 2 in accordance with template standards.
1.1 Synopsis	Sentence revised to clarify that additional safety laboratory assessments will be performed on Day 8 and Day 22 of the first cycle (for subjects who are randomized to NS-018 and	Added at the request of South Korea regulatory authority

Section # and Name	Description of Change	Brief Rationale
	subjects who switch to NS-018 from BAT)	
	Changed 'all central laboratory test results to 'all clinical laboratory test results' in the safety analysis text	Added at the request of South Korea regulatory authority
1.1 Synopsis 1.3 Schedule of Assessments 4.1 Overall Design	Added that sites in South Korea to follow a separate schedule of assessments in Appendix 14.	Added for Clarification that South Korean sites follow a different schedule of assessments.
1.1 Synopsis, Best Available Therapy Dosage 4.1 Overall Design	Specified BAT that may be used; added text regarding use of JAK inhibitors as standard of care.	Modified for Clarification.
	Added that pacritinib is not allowed for BAT and subjects who are treated with pacritinib are not eligible to participate in the study.	Clarification.
1.1 Synopsis, Study Visits 4.1 Overall Design	Provided example of JAK inhibitor	Modified for Clarification.
1.1 Synopsis, Study Visits	Added criteria of increase in spleen volume, clarified that subjects randomized to BAT arm (already on BAT or no therapy) and moved criteria that subjects need to meet criteria of at least 24 weeks on BAT or disease progression, has not undergone splenic irradiation or splenectomy and does not meet criteria for leukemic transformation.	Modified for Clarification.
1.1 Synopsis, Study Visits 1.2 Schema, study schema 1.3 Schedule of Assessments 4.1 Overall Design	Added Investigator discretion for continuing BAT outside of the study if discontinued from the study and how long NS-018 treatment may be continued.	Modified for Clarification.
1.1 Synopsis 9.4.2 Safety Analyses	Added that both central and local laboratory test results will be summarized for each treatment group.	Modified for Clarification.
1.1 Synopsis	Added to overview of procedures timing of EQ-5D-5L.	Modified for Clarification.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Assessments	Added overview of procedures table for BAT subjects for pre- and post-Cycle 7.	Modified for Clarification.
1.3 Schedule of Assessments, footnote b	Changed to 14 days	Modified to match MRI assessment.
1.3 Schedule of Assessments, footnote g Additional assessment guidance 8.2.3 Electrocardiograms	Added in SOA that 12-lead ECG to be performed in all subjects at screening, after C1D1 for NS-018 treatment arm only, and in additional assessment guidance that only for NS-018 treatment arm; additional details added in ECG procedure section.	Modified for Clarification.
1.3 Schedule of Assessments, footnote b 8.2.1 Physical Examinations	Modified text for requirements for measurement of spleen by physical examination and timing pre-dose.	To allow for flexibility if MRI and palpation cannot be done the same day.
1.3 Schedule of Assessments, footnote d 8.2.1 Physical Examinations	Timing of spleen volume changed from 10 to 14 days.	Correction.
4.0 Study Design	Text was updated to clarify that additional safety laboratory assessments will be performed on Day 8 and Day 22 of the first cycle (for subjects who are randomized to NS-018 and subjects who switch to NS-018 from BAT).	Added at the request of South Korea regulatory authority
4.1 Overall Study Design, Best Available Therapy Dosage	Specified BAT therapies and requirements to allow use of JAK inhibitor as BAT	Modified for Clarification.
4.1 Overall Study Design, Study Visits	Added increase in spleen volume criteria.	Preliminary results of this study indicated this to be relevant clinical marker.
4.2 Scientific Rationale for Study Design	Added year and version for NCCN clinical practice guidelines	Updated guidelines available.
4.3 Justification for Dose	Removed previous text and added available data from completed Phase 1 part of Study NS-018-101, recommendations of Safety Review Committee for justification of dose in this study.	Clarified justification for the dose selection of NS-018 300 mg BID in this study (Study NS-018-201).

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	#6 Removed "average" for platelet count and modified timing.	Modified for Clarification.
	#15 In addition to no investigational agent within 28 days, added number of half-lives and criteria of which to use.	Modified for Clarification.
5.1 Inclusion Criteria #16	Modified contraception language requirements.	To align with CTFG requirements and FDA guidance for genotoxic drugs of 180 days.
5.2 Exclusion Criteria #1	Added "including active tuberculosis infection."	Requested by South Korean regulatory authority.
5.2 Exclusion Criteria #2	Added contraindication language for BAT	Modified for Clarification.
5.2 Exclusion Criteria #4	Added hypersensitivity to NS-018 or excipients.	Modified for Clarification.
4.1 Overall Design Table 3	Modified BAT reference from manufacturer's information to product label throughout.	Modified for Clarification.
6.5 Concomitant Therapy	Added guidance to follow product label of any comparator therapies.	Modified for Clarification.
8.0 Study Assessments and Procedures	Text was updated to clarify that additional safety laboratory assessments will be performed on Day 8 and Day 22 of the first cycle (for subjects who are randomized to NS-018 and subjects who switch to NS-018 from BAT)	Added at the request of South Korea regulatory authority
8.0 Study Assessments and Procedures	Added that additional visits required for subjects in South Korea and cross reference to Appendix 14.	Additional assessments added at the request of South Korea regulatory authority and are specific to this country.
8.1.3 Bone Marrow 8.2.4 Clinical Laboratory Safety Assessments	Subjects transitioning from BAT to NS-018 before or at Cycle 7 Day 1 will follow the same visit schedule as subjects randomized to NS-018	Modified for Clarification.
8.1.6.1 Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form (F-SF) 7b	Added that assessment to be performed as defined in SOA and including all subjects transitioning from BAT to NS-018.	Modified for Clarification.
8.2.1 Physical Examinations	Modified text for physical examination details; added window for measurement relative to first dose.	Modified for consistency with Schedule of Assessments.

Section # and Name	Description of Change	Brief Rationale
8.2.4 Clinical Laboratory Assessments	Sentence revised to clarify that except for the assessments on Day 8 and Day 22 of the first cycle, all other safety laboratory assessments will be performed at the central laboratory	Added at the request of South Korea regulatory authority
8.2.4 Clinical Laboratory Assessments Appendix 3	Added that additional visits required for subjects in South Korea and tests to be performed by local vs. central laboratory.	Added at the request of South Korea regulatory authority and are specific to this country.
8.3.6 Adverse Events of Special Interest	Removed extrapulmonary and added development of TB. Added reference to Appendix 4.	Modified to collect any development of tuberculosis not only extrapulmonary tuberculosis. Reference to Appendix 4 added to guide to definition of AESI.
Section 9.4.2. Safety Analysis	Changed 'all central laboratory test results to 'all clinical laboratory test results' in the safety analysis text	Added at the request of South Korea regulatory authority
Appendix 2	Removed contact information for medical monitor and sponsor medical representative.	Removed in accordance with template standards.
Appendix 2, Administrative Structure	Changed imaging and ECG collection, review, and analysis to Clario.	Changed vendors.
Appendix 2, Data Quality Assurance	Records retention changed to 10 years.	Changed per current NSP records retention policy.
Appendix 2, Study and Study Center Closure	Added requirements regarding unjustifiable risk, new scientific evidence, sponsor/regulatory request, insufficient recruitment, and withdrawal of license to manufacture.	Clarified additional requirements.
Appendix 3	Sentence revised to clarify that all tests detailed in Table 8 will be performed by the central laboratory at all timepoints, except for the assessments on Day 8 and Day 22 of the first cycle, and the screening test for latent tuberculosis, which will be performed by the local laboratory.	Added at the request of South Korea regulatory authority
	Table updated to include latent tuberculosis test at screening	Added at the request of South Korea regulatory authority

Section # and Name	Description of Change	Brief Rationale
Appendix 6	Added to notes, failure rate clarification and modified guidance to 180 days post last dose for WOCBP; extended sperm donation interval, abstinence from intercourse for male subjects with WOCBP, and female subject contraception requirements (removed hormonal contraception) for participation in the study.	Modified to harmonize the protocol language related to contraception per Clinical Trials Facilitation Group (CTFG) guidance and has been aligned to harmonize with EU submissions.
Appendix 13	Modified requirements from central review to local assessment of bone marrow.	Clarified bone marrow assessments will be done locally.
Appendix 14	Added schedule of assessments specific to South Korea.	Provided study assessments schedule to address requests made by South Korea regulatory authority.
Appendix 14	Schedule of Assessments was revised to indicate that additional safety laboratory assessments will be performed on Day 8 and Day 22 of the first cycle (for subjects who are randomized to NS-018 and subjects who switch to NS-018 from BAT)	Added at the request of South Korea regulatory authority
	A test for latent tuberculosis was added at screening	Added at the request of South Korea regulatory authority

Appendix 19 Signature of Investigator

PROTOCOL TITLE: A Phase 2b, Open-label, Multicenter, Randomized, Controlled, 2-Arm Study to Assess the Efficacy and Safety of Orally Administered NS-018 Versus Best Available Therapy in Subjects with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis with Severe Thrombocytopenia (Platelet Count <50,000/μL)

PROTOCOL NO: NS-018-201

VERSION: Protocol Version 3.0

This protocol is a confidential communication of NS Pharma, Inc, I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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